1.0 Abstract

Title

Real World Evidence of the Effectiveness of Paritaprevir/r – Ombitasvir, ± Dasabuvir, ± Ribavirin in Patients with Chronic Hepatitis C in the Russian Federation - An Observational, Multi-Center Study

Keywords

Chronic HCV infection, IFN-free therapy, direct-acting antivirals (DAA), ribavirin, quality of life, resource utilization, sustained virological response (SVR).

Rationale and Background

The interferon-free combination regimen of Paritaprevir/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.

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 everyday clinical settings, which means evaluating its effectiveness. This observational study was the first effectiveness research examining the Abbvie regimen ± RBV, used according to local label, under real world conditions in the Russian Federation in a clinical practice patient population.

During the last decade when dual therapy with pegylated interferon (pegIFN) plus RBV was standard of care for the treatment of CHC, the discovery of predictive factors for virological response and the subsequent development of treatment algorithms marked a milestone in patient care for CHC. Treatment could be effectively targeted to patients most likely to respond. Many of the now well established predictors of response to pegIFN/RBV and first generation direct acting anitvirals (DAAs) in combination with pegIFN/RBV were not predictive of outcome in the development trials of the Abbvie regimen ± RBV. This observational study was planned to fill the data gaps through identifying predictive factors of response that are important in real world treatment settings. This could assist in further optimizing treatment with the interferon-free Abbvie regimen ± RBV in the future.

The aim of this observational study was to provide evidence of the effectiveness, patient reported outcome, work productivity and healthcare resource utilization of the Abbvie regimen ± RBV in a real world setting across clinical practice patient populations.

Research Question and Objectives

Research Question: What is the effectiveness, patient reported outcome, work productivity and healthcare resource utilization of the interferon-free Abbvie regimen ± ribavirin (RBV) in patients with chronic hepatitis C (CHC) in a real life setting across clinical practice patient populations?

Primary Objective: To describe in routine clinical practice the effectiveness of the interferon-free Abbvie regimen ± RBV in patients with CHC as evidenced by SVR12.

Secondary Objectives

- To provide real world evidence for predictive factors of virological response.
- To collect information on co-morbidities and concomitant medication in the Russian population.
- To describe the tolerability of the Abbvie regimen ± RBV.
- To document the effect of the Abbvie regimen ± RBV on patient-reported outcomes (PRO) and work productivity in the Russian population.
- 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.

The prescription of a treatment regimen was at the discretion of the physician in accordance with local clinical practice and label, was independent from this observational study and preceded the decision to offer the patient the opportunity to participate in this study.

Adult patients chronically infected with HCV, receiving the interferon-free Abbvie regimen were offered the opportunity to participate in this study during a routine clinical visit at the participating sites. Patients were observed for the duration of the Abbvie regimen therapy and for up to 24 weeks after treatment completion. The observational study period entailed the following data collection schemes:

- 12-week treatment regimen: four visits and two interim data collection windows;
- 24-week treatment regimen: four visits and three interim data collection windows.

Follow-up visits, treatment, procedures and diagnostic methods followed physicians' routine clinical practice. The observational period for patients receiving 12 weeks of Abbvie regimen was maximum 36 weeks (12 weeks treatment and 24 weeks post-treatment observation). For patients receiving 24 weeks of Abbvie regimen the observational period was maximum 48 weeks (24 weeks treatment and 24 weeks post-treatment observation).

Setting

For the purpose of this program, participants were recruited and observed in 16 clinical sites in the Russian Federation. University centers and outpatient clinics qualified by training and experience in the management of patients with CHC participated in this study. The inclusion period was approximately 8 months and the observational period of the study was from baseline visit until 24 weeks post-treatment.

Subjects and Study Size, Including Dropouts

The target population consisted of:

- treatment-naïve or -experienced adult male or female patients with confirmed CHC, genotype 1, receiving combination therapy with the interferon-free Abbvie regimen ± RBV according to standard of care and in line with the current local label;
- if RBV was co-administered with the Abbvie regimen, it was prescribed in line with the current local label (with special attention to contraception requirements and contraindication during pregnancy);
- patients with voluntarily signed and dated informed consent prior to inclusion into the study;
- patients not participating or intending to participate in a concurrent interventional therapeutic trial.

158 patients were planned to be enrolled during the inclusion period.

Variables and Data Sources

Primary Variable

The percentage of patients achieving SVR12 (HCV ribonucleic acid (RNA) < 50 IU/mL 12 weeks [i.e. ≥ 70 days] after the last actual dose of the Abbvie regimen).

Secondary Variables

- Co-morbidities and concomitant medication
- Serious and non-serious adverse events and pregnancy occurrences
- Questionnaires on PROs: European Quality of Life Scale (EuroQol) 5 dimension 5 level (EQ-5D-5L) questionnaire and Work Productivity and Activity Impairment (WPAI) questionnaire prior to treatment initiation, at end of treatment (EoT) as well as 12 and 24 weeks after EoT
- Patient Activation Measure (PAM)-13, Patient Support Program (PSP) satisfaction and utilization questionnaires

Data Sources

Source documents were defined as original documents. The investigator documented patient data in his/her own patient files, which served as source data for the study.

Results

One hundred fifty eight (158) adult patients with confirmed CHC, genotype 1, receiving combination therapy with the IFN-free Abbvie regimen ± RBV, according to standard of care were enrolled at 16 study centers. 63 patients received the Abbvie regimen in combination with RBV, and 95 patients were treated with Abbvie regimen without RBV.

The study population included male and female (49.4% and 50.6%) patients in the age range between 25 and 80 years, with the mean age of 48.1 ± 11.69 years (median 49.0). 83.3% patients in the overall population did not consume alcohol.

Duration of the HCV infection diagnosis was from 0 to 33 years (mean (± SD) 8.7 ± 7.25 years, median 7.5) with average duration shorter in the RBV-free group for about 2 years. From 92.1% to 100% patients in both groups had 1b genotype infection.

Fifty seven (57) patients had liver cirrhosis (Child Pugh A class), 56 on the Abbvie regimen + RBV and one on regimen without RBV, with 1b genotype, 22 of 57 patients being treatment-experienced. Nineteen (19) patients with cirrhosis were previously treated with INF + RBV regimen, 3 patients previously received INF + RBV + DAA. No patients had decompensation of the liver function. One patient in the Abbvie regimen + RBV treated group had HIV co-infection. In the Abbvie regimen - RBV treated group,

one patient (1.1%) had hepatitis B co-infection and 2 (2.2%) had HIV-co-infection. Liver and/or CHC related co-morbidities (cryoglobulinaemia, hepatic steatosis, autoimmune dermatitis) were reported in 10 (15.9%) and 6 (6.5%) of patients in the Abbvie regimen + RBV and - RBV groups, respectively. The most common other co-morbidities in both groups (> 10%) were different gastrointestinal (26.3%/ 57 records), vascular (22.4%/ 37 records), hepatobiliary (16.0%/ 27 records) disorders and metabolism and nutrition disorders (14.7%/ 27 records).

53 (34.0%) patients of the population surveyed were treatment-experienced; the proportion of treatment-experienced patients was similar in two groups, i.e. 34.5% and 33.3%. All treatment-experienced patients previously received IFN, mostly pegylated, and almost all of them (51 of 52) received RBV.

Effectiveness

All patients were receiving Abbvie regimen with or without RBV according to physician's prescription and local label. Duration of treatment was 12 weeks for all patients. Patients were highly adherent to treatment.

Primary outcome (SVR12 response) based on local assays results (excluding 8 (5.1%) patients with missing SVR12 data) was achieved in 59 (98.3%) patients [95% CI: 91.1 - 100] in the Abbvie regimen + RBV group and 87 (98.9%) patients [95% CI: 93.8 – 100] in the Abbvie regimen only group.

Two (2) (1.4%) patients were SVR12 non-responders [95% CI: 0.2 – 4.8], including one patient with relapse treated with Abbvie regimen only, and one patient with failure to suppress treated with Abbvie regimen + RBV.

Proportions of patients achieving SVR24 (single last HCV RNA < 50 IU/mL or undetectable/negative 24 weeks after the last actual dose) were similar between groups: 95.0% [95% CI: 86.1 – 99.0] in the Abbvie regimen + RBV group and 95.5% [95% CI: 88.8 – 98.7] in the Abbvie regimen only group.

Proportions of patients with virological response (HCV RNA < 50 IU/mL or undetectable/negative) at EoT were 95.0% [95% CI: 86.1 – 99.0] in the Abbvie regimen + RBV group and 96.6% [95% CI: 90.4 – 99.3] in the Abbvie regimen only group.

Negative predictor of achieving SVR12 was shown to be PT (INR) baseline values both in treatment-experienced patients (OR = 0.000 [95% Wald CI: 0.000 - 0.865], p = 0.0464) and in the overall population (OR = 0.005 [95% Wald CI: 0.000 - 0.495], p = 0.0240). In

treatment-naïve patients, creatinine clearance baseline value may be a positive predictor of achieving SVR12 (OR = 1.024 [95% Wald CI: 1.001 - 1.048], p = 0.0381).

In the overall population surveyed, achieving response at EoT was negatively associated with baseline PT (INR) values (OR = 0.000 [95% Wald CI: 0.000 - 0.024], p = 0.0013), the same association was found in patients treated with RBV (OR = 0.000 [95% Wald CI: 0.000 - 0.077, p = 0.0078) and patients with liver cirrhosis (OR = 0.000 [95% Wald CI: 0.000 - 0.055], p = 0.0064). In treatment-experienced patients, achieving the response at EoT was associated with baseline AST values (OR = 0.978 [95% Wald CI: 0.958 - 0.998], p = 0.0303).

Predictors of failure to suppress in the overall population were baseline values of the alpha-fetoprotein, in patients treated with RBV – baseline values of PT (INR) and male gender, in patients treated without RBV – modes of HCV transmission other than blood transfusion , and in patients with cirrhosis (Child Pugh class A) – male gender and baseline PT (INR).

Patients treated with Abbvie regimen only or in combination with RBV had improvements of the general quality of life and level of activation as assessed with EQ-5D-5L and PAM-13 questionnaires. There were no significant differences between regimens in the effect on EQ-5D-5L scores and patient activation in the course of the study. Patients treated with Abbvie regimen only or in combination with RBV had improvements of the work productivity and activity as assessed with WPAI Hep C v2.0. questionnaire.

60.3% of patients participated in the patient support program and found it fully or mostly addressing their needs. The majority of patients utilized printed materials at least once weekly and reported their level of satisfaction with the program as very good, good or satisfactory.

Safety

Adverse events were registered in 31 (19.6%) patients (41 events). The proportion of patients with AEs and the number of AEs as well as their severity were higher in the Abbvie regimen + RBV treated patients.

The most affected SOC was general disorders and administration site conditions (16 events in 13 (8.2%) patients), followed by infections and infestations (8 events in 8 (5.1%) patients), blood and lymphatic system disorders and gastrointestinal disorders (3

events in 3 (1.9%) patients for each category), hepatobiliary disorders (3 events in 2 (1.3%) patients) and skin and subcutaneous tissue disorders (2 events in 2 (1.3%) patients).

The majority of patients had mild AEs (24 (15.2%) patients/ 33 events), 5 (3.2%) patients had 5 AEs of moderate intensity, and 2 (1.3%) patients developed 3 severe events. There were 4 events of moderate severity in the Abbvie regimen + RBV treatment group (thrombocytopenia, arrhythmia, sinusitis, hepatocellular carcinoma); one AE was in the Abbvie regimen - RBV treatment group (hepatitis C).

16 (10.1%) patients experienced 21 events assessed as related to the therapy with Abbvie regimen (abdominal discomfort, diarrhea, nausea, asthenia, fatigue, hepatic pain, hepatitis C [verbatim terms: relapse after antiviral therapy, virologic breakthrough], blood bilirubin increased, headache, pruritus).

9 (14.3%) patients experienced 11 AEs related to RBV administration (asthenia, anaemia, thrombocytopenia, hyperbilirubinaemia, jaundice, haemoglobin decreased, pruritus).

There were 2 SAEs in the study reported in 2 (1.3%) patients, arrhythmia and hepatocellular carcinoma. Both SAEs were registered in the Abbvie regimen + RBV treated patients, were moderate by severity and were not related to the Abbvie regimen.

Discussion

The results obtained in this study support data of the previous interventional studies of the Abbvie regimen. The results of this study demonstrate that treatment of CHC 1 genotype patients with Abbvie regimen with and without ribavirin for 12 weeks is effective and well tolerated in routine clinical practice. Both regimens help achieve SVR12 and SVR24, with low non-responders rates, and improve patients' quality of life and activity. Abbvie regimen without ribavirin for 12 weeks had more favorable safety profile than ribavirin-containing regimen.

Marketing Authorisation Holder(s)

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