1. Abstract

Title

A follow-up study to assess the durability of response and persistence of resistance to AbbVie's 2 direct-acting antiviral agent (2D) therapy in Japanese subjects who participated in Phase 2 or 3 clinical studies for the treatment of chronic hepatitis C virus (HCV) infection

Keywords

HCV, DAA, ombitasvir/ paritaprevir/ ritonavir, VIEKIRAX, Japan

Rationale and Background

Rationale

Japanese clinical studies for the AbbVie's 2D regimen have been conducted to evaluate the efficacy by follow-up for up to 48 weeks after the treatment. After conclusion of the studies, the durability of SVR and the potential resistance to AbbVie's 2D regimen was assessed for 4 years in this PMOS. Thus, this is the first study evaluating both the long-term durability of SVR and persistence of Resistance-associated variants (RAVs) following the treatment with AbbVie 2D regimen in Japan. In addition, the incidence of cirrhosis and liver cancer was monitored because patient age is much higher than that in other countries.

Background

The 2D regimen with ombitasvir/ paritaprevir/ ritonavir was approved for treatment of HCV GT1 infections in September 2015 and also was launched to the market in November 2015 as a third IFN-free regimen in Japan.

Research Questions and Objectives

Assess the durability of SVR in subjects who achieved SVR12 by treatment with AbbVie's 2D regimen (ombitasvir/ paritaprevir/ ritonavir).

Endpoints

- ✓ Safety endpoints
  - Assess the number of SAEs
- ✓ Efficacy endpoints
  - Assess the durability of SVR in subjects who achieved SVR12.
  - Assess the persistence of RAVs in subjects who experience virologic failure.
  - Monitor the incidence of cirrhosis and liver cancer.

Study Design

This was a follow-up study to assess the durability of response and persistence of resistance and to ombitasvir/ paritaprevir/ ritonavir in Japanese patients who have participated in Phase 2 or 3 clinical studies with these agents for the treatment of Chronic Hepatitis C.

Setting

Study Period

Registration period

- From September 2015 to June 2017

Study period

- From September 2015 to February 2020

Investigative Sites

About 50 sites for participated in the studies M12-536 study or M13-004 study.

Study medication

This was a follow-up study for M12-536 study or M13-004 study. Therefore, there was no study medication after the clinical studies.

Observation Period

4 years after 48 weeks follow-up period of M12-536 study or M13-004 study.

Subjects and Study Size, Including Dropouts

Subject

- The subjects were the chronic HCV infection that met the following criteria.

Study Size

- 436 patients at maximum who were dose with 2D in the M12-536 study or M13-004 study

Inclusion Criteria

- The subjects who have been treated with 2D regimen (ombitasvir/ paritaprevir/ ritonavir) and completed 48 weeks of follow up from the prior Phase 2 or 3 studies in Japan.
- The subjects who agree to sign the informed consent.

Exclusion Criteria

- The subjects who treated with DAA immediately after or during post-treatment period of M12-536 study or M13-004 study.

Variables and Data Sources

Variables

1) Patient information obtained during M12-536 study or M13-004 study.

2) Following information since completion of M12-536 study or M13-004 study

（1） Medications for the treatment of CHC

（2） Effectiveness evaluation

（3） Occurrence of cirrhosis and liver cancer

（4） HCV resistance test for detection of RAVs

（5） Risk factors of HCV re-infection

（6） Serious adverse events

（7） Discontinuation of survey

Data Sources

The original data source for this PMOS was medical records retained by medical institutions participating in this PMOS. Physicians completed registration form and case report form prepared by AbbVie.

For some survey questions, such as those listed below, the information provided in CRF was the original data source.

- observations
- assessments

Results

Out of 436 patients who were dose with 2D in the M12-536 study or M13-004 study, 345 patients were enrolled in this PMOS. The CRF were collected from 345 patients. 11 patients were excluded from the safety analysis set due to the inclusion/exclusion criteria ; therefore 334 patients were included in the final safety analysis set. The disposition of patients excluded from safety analysis set was "unevaluable for safety" in 2 patients, "DAA Use during previous clinical study" in 1 patient and "No data" in 10 patients. 2 out of 10 also had "unevaluable for safety" and "DAA Use during previous clinical study", respectively. Of these 11 excluded patients, there were no SAEs.

Of the 334 patients in the safety analysis set, 4 patients were excluded from the efficacy analysis set, therefore 330 patients were included in the final efficacy analysis set. The 4 patients had no evaluation for liver cancer (Figure 1).

Safety

28 SAEs occurred in these 25 patients and the rate of SAEs was 7.5% (25/334) (Table 8).

In Table 8, when the same event occurred in one patient, it was counted as one event. Two hepatocellular carcinoma were developed in one patient, and Table 9 shows a total of 29 SAE. Of the 29 events, 26 had an outcome of "recovered/recovering", 2 were "deaths", and 1 was "unknown" (Table 9).

See section 10.4.1.2. for "endocarditis" and section 10.6.3 for "death".

Effectiveness

The relapse rate of SVR at the end of study was 0% (0/318) (Table 10).

During the observation period, 10 cases of liver cancer were confirmed and the rate of liver cancer at the end of the study was 0.7 events/100 PYs. Of the 10 liver cancers, 7 occurred within 2 years after the last dose (Table 11). The rate of liver cancer was 2.7 events/100 PYs in patients with compensated cirrhosis and 0.5 events/100 PYs in patients without cirrhosis (Table 12). The rate of liver cancer was 0.5 events/100 PYs in patients who achieved SVR12 and 9.1 events/100 PYs in patients who did not achieved SVR12(Table 13). In patients who achieved SVR12, the rate of liver cancer was 2.2 events/100 PYs in patients with compensated cirrhosis and 0.3 events/100 PYs in patients without cirrhosis (Table 16).

During the observation period, 3 cases of cirrhosis were confirmed and the rate of cirrhosis at the end of the study was 0.2 events/100 PYs (Table 15).

There were statistically significant difference in developing liver cancer in below factors:

For efficacy analysis set

Age, platelet count, albumin level, cirrhosis, SVR12, SVR at end of clinical study, diabetes, Fib-4 index, IL28 B, hepatoprotective drug

For patients with compensated cirrhosis in efficacy analysis set

end of study SVR, Age, albumin level, LLOQ at 4 weeks after last dose

For patients without cirrhosis in efficacy analysis set

SVR12, SVR at end of clinical study, weight, hepatoprotective drug

There were statistically significant difference in developing cirrhosis in below factors:

Gender, Fib-4 index , IL28 B

Discussion

The SVR achieved with VIEKIRAX treatment was sustained over a long period, indicating that the development of cirrhosis and HCC was suppressed in patients with any background. The occurrence of HCC was suppressed in both cirrhotic and non-cirrhotic patients; however, the occurrence of HCC was higher in cirrhotic patients, indicating that HCV should be treated early.

In conclusion, this PMOS results indicate that SVR achieved with VIEKIRAX treatment was sustained over a long period and early initiation of treatment is beneficial in HCV patients.

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Not applicable