1. Abstract

Title

Drug use-results survey in patients infected with hepatitis C virus genotype 2

Keywords

HCV, DAA, paritaprevir/ritonavir/ombitasvir, Viekirax, V/E, ribavirin, Rebetol, RBV, real world, Japan

Rationale and Background

[Rationale]

In general, the Pharmaceuticals and Medical Devices Agency (PMDA) requests pharmaceutical companies to collect data on the safety and effectiveness of new drugs in routine daily practice.

When the Viekirax (V/E: paritaprevir/ritonavir/ombitasvir) co-administrated with Rebetol (RBV: ribavirin) was approved for treatment of HCV genotype 2 (GT2), PMDA requested that "The applicant is required to develop and appropriately implement a risk management plan." as the approval condition for the new indication.

This study evaluated appropriate use of this regimen as described in the J-RMP which was to collect data on the safety and effectiveness of Viekirax co-administrated with Rebetol in daily practice.

[Background]

AbbVie regimen of paritaprevir/ritonavir/ombitasvir was approved for treatment of HCV GT1 in September 2015 and was launched to the market in November 2015 in Japan as the third IFN-free regimen.

And paritaprevir/ritonavir/ombitasvir co-administered with ribavirin was approved for treatment of HCV GT2 in September 2016 in Japan as an IFN-free regimen.

Objectives

To evaluate the safety and effectiveness of Viekirax coadministered with Rebetol used for chronic hepatitis C patients of genotype 2

Study Design

This is a prospective, multi-center, post-marketing observational study (PMOS).

Setting

238 investigative sites were contracted with AbbVie GK to conduct this study, and 170 of these sites enrolled patients into the study. Recruitment period was from September 2016 to February 2018.

Viekirax and/or Rebetol was only be prescribed to patients as per Japan label by a physician with sufficient knowledge and experience in the treatment of hepatic viral disease.

The recommended oral dose in adults is two tablets (25 mg ombitasvir, 150 mg paritaprevir and 100 mg ritonavir) of Viekirax once daily after a meal for 16 weeks in combination with Rebetol (200 mg ribavirin).

The observational period consisted of treatment period (16 weeks) and follow-up period (24 weeks). The data gathered in daily practice was collected in this study.

Patients and Study Size, Including Dropouts

[Patients]

Inclusion criteria

HCV genotype 2 patients treated with Viekirax (paritaprevir/ritonavir/ombitasvir) coadministered with Rebetol (ribavirin) in daily practice

Exclusion criteria

Patients who have been previously treated with paritaprevir/ritonavir/ombitasvir and ribavirin

[Study Size]

480 patients (As enrollment patients)

Variables and Data Sources

[Variables]

Safety

Adverse drug reactions (ADRs), serious adverse events (SAEs)

ADRs of special interest;

"fluid retention", "hepatic disorder, hepatic failure", "anaemia", and "acute renal failure"

Clinical laboratory tests;

Hematology;	WBC, RBC, Hemoglobin, PLT
Blood chemistry;	ALT, AST, ALP, Albumin, total/direct-Bilirubin, Creatinine, BUN
Other;	Alpha Fetoprotein

Effectiveness

Primary variable;

- ✓ SVR12

Secondary variables;

- ✓ SVR24
- ✓ On-treatment virologic failure (no response, partial response, breakthrough)
- ✓ After-treatment virologic failure (relapse)
- ✓ Time course of the measurements of effectiveness
- ✓ Factors that may affect the effectiveness

[Data Source]

Data source in this study was from institute's medical chart. Participating physicians in this study transcribed the data from medical chart to Case Report Form (CRF) which AbbVie prepared. If the event fulfilled the serious criterion (Serious Adverse Event), the "Serious Adverse Event Report" form was completed additionally.

Results

The number of contract sites was 453, and the number of enrolled patients was 449. The safety analysis set (of the enrolled patients, patients who did not meet any

of the exclusion criteria[1]) included 429 patients and the effectiveness analysis set included 344 patients.

[Safety]

The rates of related adverse event, adverse drug reactions (ADRs) was 38.93% (167/429), refer to **10.6.1 Adverse Drug Reactions (ADRs)**.

The rates of ADRs in the clinical trial conducted in Japan (M14-153) was 50.0% (80/160). i) The rates of ADRs in this study was not higher than that in the clinical trial conducted in Japan.

The rates of ADRs of special interest (refer to **10.6.4 ADRs of Special Interest**) in this study were 0.47% (2/429) for "Fluid retention", 14.45% (62/429) for "hepatic function disorder/hepatic failure", 24.94% (107/429) for "anaemia", and 1.86% (8/429) for "acute renal failure". Most common (over 10 events) of "hepatic function disorder/hepatic failure" were blood bilirubin increased (8.86%) or hyperbilirubinemia (2.56%). And, most common (over 10 events) of "anaemia" were anaemia (18.65%) and haemoglobin decreased (6.06%) in. There was no new safety concern regarding clinical laboratory tests.

The rates of Serious Adverse Event (SAEs) was 2.10% (9/429), refer to **10.6.2 Adverse Events (AEs)**. 12 SAE, "altered state of consciousness" and "drug-induced liver injury" each in 0.47% (2/429) and "decreased appetite" , "pleural effusion", "nausea" , "erythema multiforme", "oedema peripheral" , "blood bilirubin increased" , "hemoglobin decreased" and "femur fracture" each in 0.23% (1/429), occurred in these 9 patients. The outcomes of these were recovered or recovering.

[Effectiveness]

SVR12 rate, the primary effectiveness variable, was 93.31% (321/344, 95% CI: 90.14 -95.71), refer to **10.4.1 Primary Effectiveness Variable (SVR12)**.

This rate was slightly higher than the SVR12 rate in patients with GT2 of 91.5% (43/47, 95% CI: 83.5-99.5) in the clinical trial conducted in Japan(M14-153). i)

Combination therapy of Viekirax and Rebetol therapy used for chronic hepatitis C

1 Violation of contract, Protocol violation, Registration violation, Duplicate cases, Patients who have not received this drug, Patients without information after the date of administration of this drug, Patients for whom safety could not be evaluated

patients of genotype 2 has been shown to be highly effective in the real world.

Discussion

The results of this observational study support the safety and effectiveness of Viekirax coadministered with Rebetol used for patients infected with HCV genotype 2 in routine daily practice in Japan. The safety results of this study were consistent to the currently documented safety profile of the product, as described in the label and periodic safety update reports.

Marketing Authorisation Holder(s)

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