Abstract

Title

A Study to Evaluate the Risk of De Novo Hepatocellular Carcinoma in Patients with Compensated Cirrhosis Treated with Direct-Acting Antivirals for Chronic Hepatitis C (De Novo DAA PASS)

Keywords

Direct-acting antiviral agent (DAA), cirrhosis, hepatitis C virus (HCV), de novo, hepatocellular carcinoma (HCC), sustained virologic response (SVR), United States Department of Veterans Affairs (VA)

Rationale and Background

In December 2016, 4 Marketing Authorization Holders (MAHs) (AbbVie, Bristol Myers Squibb [BMS], Gilead Sciences [Gilead], Janssen-Cilag International NV [Janssen]), subject to the Pharmacovigilance Risk Assessment Committee (PRAC) requirement from a procedure under Article 20 of Regulation (EC) No 726/2004 (EMEA/H/A-20/1438), began to assess hepatitis C virus (HCV) registries and databases worldwide in order to determine the feasibility of using existing data sources to evaluate the potential risk of de novo hepatocellular carcinoma (HCC) following direct-acting antiviral agent (DAA) treatment in HCV-infected patients with compensated cirrhosis (Child-Pugh class A; CP-A) without a history of diagnosed HCC. Merck Sharp & Dohme (MSD) received formal regulatory notification March 2017 to adhere to the outcome of the Article 20 referral procedure, and at that time joined the MAH's consortium. Following the withdrawal of the European Union (EU) license for Olysio (simeprevir), Janssen is no longer part of the procedure, but data from use of simeprevir are included in the analysis of DAA-treated patients. Bristol Myers Squibb chose not to renew their marketing authorization for Daklinza

(daclatasvir), but data from use of daclatasvir are included in the analysis of DAA-treated patients.

After interactions with the PRAC summarizing available literature and data sources and demonstrating an absence of increased risk of de novo HCC associated with DAA exposure, the MAHs agreed to generate a report on de novo HCC risk following DAA exposure relative to patients treated with interferon (IFN)-containing regimens or untreated chronic hepatitis C patients within the United States Department of Veterans Affairs (VA) cohort to address the PRAC's safety concern. In their Assessment Report dated 11 January 2018, adopted by the Committee for Medicinal Products for Human Use (CHMP) on 25 January 2018, the PRAC agreed that "A post-authorisation safety study to investigate the impact of DAA therapies on the incidence and type of de novo HCC is feasible using the Veterans Health Administration Cohort as a secondary data source."

Research Question and Objectives

This analysis examined the following research question: among compensated cirrhotic patients, does DAA therapy for chronic HCV infection increase the risk of incident HCC compared to no treatment or treatment with IFN-based regimens?

The primary objectives of this study were as follows:

1. Estimate the risk of de novo HCC associated with DAA therapy exposure in cirrhotic HCV patients compared to no anti-HCV therapy exposure in cirrhotic HCV patients.
2. Estimate the risk of de novo HCC in cirrhotic HCV patients treated with DAA therapy compared to those treated with IFN-based therapy.

The secondary objective was to compare, in a subset of patients with available data recorded in the VA Central Cancer Registry (CCR), tumor characteristics (i.e., tumor size, tumor stage, and receipt of treatment) of the de novo HCC cases observed

following initiation of DAA therapy to those of de novo HCC cases observed (a) following initiation of IFN-containing regimens and (b) in untreated patients.

Study Design

A retrospective cohort study of HCV infected patients seeking care in the VA system was conducted. The primary analyses for this study were:

1. Evaluate the impact of DAA therapies on the risk of de novo HCC in HCV infected patients with compensated liver cirrhosis without a history of diagnosed HCC compared to no anti-HCV therapy exposure, and
2. Evaluate the risk of de novo HCC among patients who received IFN-free DAA therapy relative to historical controls in the same dataset who received IFN-based therapy.

For the secondary objective, tumor characteristics were compared between the HCV DAA treatment group and both 1) the HCV IFN-treated group and 2) the untreated group.

Setting

This was a retrospective cohort study conducted among United States veterans with chronic HCV who sought care at any of the medical centers and ambulatory care and community-based outpatient clinics that comprise the national VA healthcare system.

Subjects and Study Size, Including Dropouts

Patients were United States veterans, aged 18 years or older, with chronic HCV defined as a positive test for HCV ribonucleic acid (RNA) in plasma by qualitative or quantitative assays or genotype test between January 01, 2005 and December 31, 2017. The analysis was restricted to HCV mono-infected (i.e., no hepatitis B virus [HBV] or human immunodeficiency virus [HIV] coinfection)

patients with compensated liver cirrhosis. Within the VA healthcare system, all HCV-infected patients were eligible for HCV treatment during the study period, and there were no limitations to DAA availability based on income, fibrosis stage, or psychosocial disorders.

For the first primary objective, the study cohort included 65,353 patients of whom 53,847 patients contributed to untreated time and 27,147 patients contributed to DAA time. Some patients (N = 15,641) contributed to both untreated and DAA exposed time. For the second primary objective, the study cohort included 33,943 patients of whom 6,809 patients were exposed to IFN treatment and 27,134 patients were exposed to DAA only regimens.

Variables and Data Sources

The index date defined the start of de novo HCC risk.

For the first primary objective, the index date for untreated time was the date of the first clinical encounter (i.e., office visit, procedure, lab result, prescription, etc.) recorded from July 01, 2012 to December 31, 2017, inclusive. This served as the start of untreated time in both patients who were never treated and patients who were as yet untreated as of the first clinical encounter. The index date for DAA exposed time was the start of DAA therapy.

For the second primary objective, the index date was the date of initiation of first IFN treatment between January 01, 2005 and December 31, 2013 for IFN-treated patients and the date of initiation of the first DAA treatment between January 01, 2014 and December 31, 2017 for DAA-treated patients.

De novo HCC diagnosis was defined based on a hierarchical approach. First, patients were classified as having HCC based on presence of HCC diagnosis in VA CCR. For the remaining patients, patients were identified as having HCC if they had > 1 instance of International Classification of Diseases (ICD)-9 (155.0) or ICD-10

codes (C22.0, C22.8, C22.9, D01.5) for HCC. Prior research has demonstrated this definition for HCC is highly valid.

Multiple covariates including demographic variables, alcohol use and drug abuse, other medical comorbidities, laboratory values, sustained virologic response (SVR), health care utilization, last prior HCV treatment, Deyo-Charlson Comorbidity Index (DCCI), and HCC surveillance were determined and used for analysis.

For the secondary objective, chi-squared tests for categorical variables and t-test for continuous variables were used for tumor characteristic comparisons, as appropriate.

The VA data sources included the following 3 registries: VA Corporate Data Warehouse (CDW), VA CCR, and VA Vital Status file.

Results

For the first primary objective, the risk of HCC associated with the DAA exposed time was significantly lower compared to untreated exposed time during the same era in both the unadjusted Cox model and in the multivariable analysis (unadjusted hazard ratio [HR]: 0.79 [95% confidence interval [CI]: 0.74 – 0.84] and adjusted HR: 0.70 [95% CI: 0.65 – 0.74]), respectively.

Among DAA-treated patients included in the cohort for the first primary objective, 24,267 patients (89.39%) achieved SVR, 964 patients (3.55%) did not achieve SVR; 1916 patients (7.06%) had missing SVR status.

For the second primary objective, the risk of HCC associated with DAA treatment was not significantly different compared with the IFN treated group in a previous time era in the unadjusted Cox model and in the multivariable analysis (unadjusted HR: 1.08 [95% CI: 0.97 – 1.20] and adjusted HR: 0.98 [95% CI: 0.87 – 1.10]).

Among patients included in the cohort for the second primary objective, 24,255 DAA-treated patients (89.39%) and 2,489 IFN-treated patients (36.55%) achieved SVR,

963 DAA-treated patients (3.55%) and 3,331 IFN-treated patients (48.92%) failed to achieve SVR; 1,916 DAA-treated patients (7.06%) and 989 IFN-treated patients (14.53%) had missing SVR status.

For the secondary objective, in a subgroup of VA patients with available information on HCC tumor characteristics, HCV-infected patients diagnosed with compensated cirrhosis and treated with DAAs who were diagnosed with de novo HCC were more likely to have an earlier stage and smaller tumor size compared with patients diagnosed with HCC who were untreated with DAAs or treated with IFN. There was no association between DAA treatment and size and stage of tumors.

Conclusion

The results from this post-authorisation safety study support an observed considerable reduction in de novo HCC risk compared to no treatment, and lack of overall differences in de novo HCC risk between DAA and IFN in a cohort of chronic HCV patients with compensated cirrhosis. In a subgroup of VA patients with available information on HCC tumor characteristics, patients treated with DAAs who were diagnosed with de novo HCC were more likely to have an earlier stage and smaller tumor size compared with patients diagnosed with HCC who were untreated or were treated with IFN. There was no association between DAA treatment and size and stage of tumors.

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IRB = internal review board; EC = ethics committee; N/A = not applicable