1 ABSTRACT

Title

DAA-PASS: A Post-Authorisation Safety Study of Early Recurrence of Hepatocellular Carcinoma in HCV-Infected Patients after Direct-Acting Antiviral Therapy

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Keywords

direct-acting antiviral, hepatitis C virus-infected, hepatocellular carcinoma

Rationale and background

Previous reports of direct-acting antiviral (DAA) therapy use for chronic hepatitis C after successful treatment of hepatocellular carcinoma (HCC) have raised concerns that DAA therapy is associated with an increased risk of early HCC recurrence with mixed results.

The European Commission requested a review of DAAs for the treatment of chronic hepatitis C to evaluate the risk of HCC recurrence, recommending that the DAA marketing authorisation holders (MAHs) should perform a prospective study to assess the risk of early recurrence of previously treated HCC after DAA therapy for hepatitis C virus (HCV).

With the widespread availability and increased prescribing of DAAs worldwide and within the 5 countries with DAA-PASS sites as of 2019, the population of patients who were naïve to DAA treatment for HCV infection after successful HCC treatment had dramatically diminished compared with the original enrollment projections provided in the original DAA-PASS protocol (version 1.0) submitted to the European Medicines Agency/ Pharmacovigilance Risk Assessment Committee (EMA/PRAC) June 2017. Depletion of the patient pool was a significant risk for this study, particularly as, soon after their introduction, many payers prioritized DAA coverage to those with advanced disease {1-3}. As this population was to be studied in DAA-PASS, DAA-naïve patients with cirrhosis became difficult to enroll. Later, payers expanded coverage to align with guidelines to allow treatment of all individuals with active HCV infection, further accelerating the depletion of the pool of DAA-naïve patients {4}.

Although enrollment remediation efforts were initiated in 2019, overall, the monthly screening and enrollment rates decreased or remained unchanged over the course of the year, likely reflecting the lack of the available eligible patient population. Thus, the final amended protocol (Protocol Version 4.2) reflected an estimated convenience sample with a maximum of 70 patients enrolled in the DAA-PASS sub-study.

In the PRAC PASS Protocol Amendment Assessment Report dated 09 April 2021, the PRAC acknowledged that low enrollment and small sample size of DAA-PASS could preclude several analyses or the MAHs' ability to obtain robust conclusions.

Study Design

This prospective, observational study was designed to estimate the risk of early HCC recurrence associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care of HCV-infected patients with previous successfully treated HCC using a prospective cohort from the TARGET-HCC Registry. DAA-PASS is a sub-study of the TARGET-HCC Registry that included a prospective cohort. The exploratory analyses reflected data from a historical cohort in Italy (i.e., Italian Liver Cancer Group [ITA.LI.CA] cohort).

Planned analyses are described in Section 4 of the statistical analysis plan (SAP) and Section 9.7 of the protocol. Analyses such as those that were to include integration with the historical cohort data were not conducted due to the small DAA-PASS sample size and limited recurrence events. The analyses presented within this final study report of the PASS reflect those deemed feasible while still presenting evidence to inform the objectives of the planned analyses.

Data for the prospective DAA-PASS cohort were obtained through abstraction of the patient medical record into the TARGET-HCC Registry database. Data for the historical cohort came from the ITA.LI.CA cohort database; data were abstracted from medical records at the time of initial HCC diagnosis and treatment; subsequent data abstractions were performed at the time of any HCC recurrence event.

For the prospective DAA-PASS cohort, patients were enrolled in the United States (US) (n=33) and Italy (n=9); patients were screened in Germany and Spain, but none were enrolled. While the study was approved by the Ethics Committee (EC) in France, no patients were screened in the country. The data collection period started 29 March 2018 (US sites only) and ended 30 June 2021 (all sites). The historical cohort was comprised of consecutive ITA.LI.CA cohort patients with co-morbid HCV and HCC, unexposed to DAAs and managed within participating centers in Italy.

Results

The 42 patients enrolled in the study were predominantly between the ages of 40 and 64 years at enrollment (66.7%) and were a median of 61.5 years old at HCC diagnosis. Patients were more frequently male (78.6%) and White (74.4%). A total of 24 patients were treated for HCV with at least 1 DAA therapy and had a median follow-up time of 3.1 months from baseline (i.e. index date) to the start of the therapy, median exposure to DAA of 2.8 months, and median follow-up time since the start of DAA therapy of 18.9 months, for a total of 62 months of DAA exposure person-time. The total median duration of DAA unexposed person-time among all patients was 7.2 months (Table 8). Only 10 (24%) HCC recurrence events were observed during the study, which corresponded to an overall crude HCC recurrence rate at 24 months of 17.7 per 100 person-years (PY) and an estimated cumulative incidence of HCC recurrence of 29%. The HCC recurrence events observed included 5 events diagnosed among those who ever received a DAA during follow-up and 5 HCC recurrence events among those who never received a DAA during follow-up, corresponding to estimated cumulative incidences of 23% and 37%, respectively. In the analysis of the primary endpoint, the crude hazard ratio (HR) for risk of early HCC recurrence (within the follow-up period after the first HCC-free image) associated with DAA therapy exposure relative to no DAA therapy exposure during routine clinical care was HR=0.6 (95% CI, 0.2-2.2). After including age in the model, the adjusted HR was 0.7 (95% CI, 0.2-2.3) (Table 14.1.11).

The ITA.LI.CA historical cohort included 522 chronic HCV-infected patients with no prior DAA exposure who met the DAA-PASS inclusion and exclusion criteria, with a median age of 71 years at incident BCLC stage A HCC diagnosis and mostly male (68.8%) (ITA.LI.CA Table 3). The median of total duration of DAA unexposed person-time was 17.9 (Interquartile range; IQR: 15.9) months (ITA.LI.CA Table 1). During 24 months of follow-up, HCC recurrence events were observed in 193 (37%) DAA unexposed patients (ITA.LI.CA Table 2) with a cumulative exposure-adjusted rate of 25 per 100 PY at 12 months, and 28 per 100 PY at 24 months (ITA.LI.CA Table 9).

Discussion

Despite the impact of the small sample size in this PASS, the DAA-PASS study did not find evidence of an increased risk of HCC recurrence among enrolled patients who were exposed to DAA therapy relative to no DAA therapy exposure. The findings in this PASS have been corroborated by other multicenter cohort studies (HEPATHER, North American Cohort, etc.) with an internal contemporaneous comparator cohort that assessed the risk of HCC recurrence in patients who achieved complete response (CR) to prior HCC-directed treatment and were subsequently treated with DAAs for chronic HCV infection.

In conclusion, this was an observational study in a well-characterized group of patients. Based on the analyses conducted in the DAA-PASS, there was no evidence to suggest exposure to DAAs was associated with an increased risk of HCC recurrence.

Marketing Authorisation Holder(s)

Joint DAA-PASS MAHs
(AbbVie Deutschland GmbH & Co. KG, Gilead Sciences Ireland UC, Merck Sharp & Dohme B.V.)