Safety of Direct Acting Antiviral Medications for Patients with Hepatitis C

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I. Objectives

The purpose of this study is to assess the rates of adverse events in patients with Hepatitis C virus (HCV) who are exposed to direct acting antivirals (DAA) compared to those not exposed to the drugs.

II. Background and Rationale

About 2.4 million Americans are infected with the HCV [Hofmeister et al., 2018]. About 28% of those with HCV have cirrhosis and annually 1-4% of those individuals will go onto develop liver cancer [Lu et al., 2018; Chen and Morgan, 2006]. Antiviral treatments for HCV previously required a combination of agents taken over 24-48 weeks, were associated with significant side effects, and were effective in about 54-63% of patients who completed a full course of treatment [Fried et al., 2002; Manns et al., 2001; Hadziyannis et al., 2004]. Thus, the advent of newer DAAs that could be taken over as little as 8-12 weeks with few significant side effects [Tao et al., 2017; Jakobsen et al., 2017] and sustained virologic response (SVR) of 93-99% across different target populations and treatment regimens [Afdhal et al., 2014a; Kowdley et al., 2014; Afdhal et al., 2014b] was hailed as a substantial breakthrough in treating HCV [Bidell et al., 2016]

Enthusiasm for DAAs was somewhat tempered by a *Boxed Warning* issued in October of 2016 by the Food and Drug Administration (FDA) about potential for reactivation of the Hepatitis B virus (HBV) [US FDA, 2016]. This report prompted an analysis by the Institute for Safe Medication Practices of the FDA's Adverse Events Reporting System (FAERS) that reported cases of liver failure (n=500) and severe liver injury (n=1000) among patients taking DAAs over the 12 months ending June 30, 2016 [Institute for Safe Medication Practices, 2017]. The authors acknowledge some of the limitations of using the FAERS data including the voluntary nature of the reporting, the lack of detailed medical history data on patients, and the possibility of some misclassification because the adverse event of interest (liver failure or liver injury) is also a significant complication of the disease. However, the number of cases and the fact that about 90% of reports were from health professionals suggested that further investigation is warranted.

Post-marketing surveillance is frequently required by the FDA as a condition of approval, particularly among new drugs that have progressed rapidly through the approval process. To enable relatively rapid surveillance, in 2008 the FDA pioneered the use of real-world evidence through the Sentinel initiative [US FDA, 2018] which complements the FAERS by enabling more in-depth investigation of safety concerns that emerge through voluntary reporting. Sentinel employs a common data model that harmonizes data on nearly 200 million people receiving care in about 18 health systems. More recently, the Patient Centered Outcomes Research Institute (PCORI) invested in developing the National Patient Centered Clinical Research Network (PCORnet) to advance the use of real-world evidence for patient-centered studies including both comparative effectiveness and safety research [Fleurence et al., 2014]. PCORnet is a large, highly representative, national "network of networks" that created a common data model based on Sentinel which harmonizes data routinely gathered in a variety of healthcare settings, including hospitals, doctors' offices, and community clinics. PCORnet includes data on about 100 million people who have received care in the last 5 years in one or more of 13 clinical data research networks. We will leverage the collaborations and rich longitudinal data from three participating health care systems in PCORnet to examine whether patients with HCV who were prescribed newer DAAs experienced higher rates of adverse events than patients with HCV who were not treated with DAAs.

III. Methods

A. Research Design

We will conduct an observational retrospective study using administrative, longitudinal electronic health record and other data collected during the normal course of patient care from 2011 to 2017 in three health systems. All participants will start in the untreated (no DAA) group and contribute exposure time to that group until they fill a prescription for a DAA at which time they will begin contributing person time to the DAA group; participants will be followed until they have the adverse event of interest or are censored (receive an older DAA, leave the health system, or end of the observation or study period). A graphical illustration of the study design is provided in Appendix 1.

B. Sample

The study will be conducted in three health systems: KP Southern California (KPSC); KP Northern California (KPNC); and OneFlorida.

Using clinical and enrollment data maintained in each participating system, the study population will include all adults between the ages of 18 and 88 who have any indication of a diagnosis of HCV (genotype, quantitative or qualitative HCV RNA result, antibody result, ICD code, or medication). The study will be restricted to those with an HCV RNA quantitative result or genotype indicating active virus after January 1, 2012, who receive care from the participating site at least one year prior to the date on which their eligibility is triggered, and who are naïve to DAA treatment at entry to the study.

C. Measurement

Exposure and Outcomes

Exposure will be calculated as person-time in the non-DAA and/or DAA group. Entry to the DAA group will be triggered on the date patients are dispensed their first prescription for a DAA. The outcomes of interest are serious adverse events: death, multiple organ failure, liver cancer, hepatic decompensation, acute-on-chronic liver event, acute myocardial infarction (AMI), ischemic or hemorrhagic stroke, arrhythmia, acute kidney failure, and hepatitis B (HBV) reactivation. We will also examine hospitalizations and emergency department visits.

The outcomes of interest will be based on several sources including those most commonly evaluated by the FDA (cardiac, liver, and kidney toxicity), the adverse events highlighted in the FAERS report that motivated this study, and clinical input from our collaborators. Outcomes will be assessed from November 2013 (the first month in which a DAA could have been prescribed) through December 2017. Patients will be followed for up to 180 days following DAA initiation to restrict the analysis to a time-period in which adverse events were most likely to be attributable to exposure to a DAA.

Covariates

Several covariates will be included in our analysis: demographics (age, gender, race, ethnicity), body mass index, smoking status, and utilization (skilled nursing, home health, emergency, inpatient). We will also include laboratory results (MELD, AST, ALT, hemoglobin A1c, albumin) and calculate an AST to Platelet Ratio Index (APRI) score [Wai et al., 2003]. We defined comorbidities using Quan's algorithms [Quan, 2005].

IV. References

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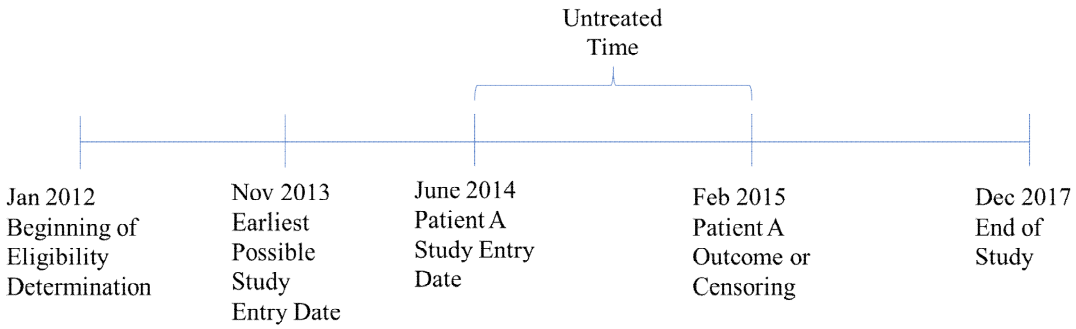
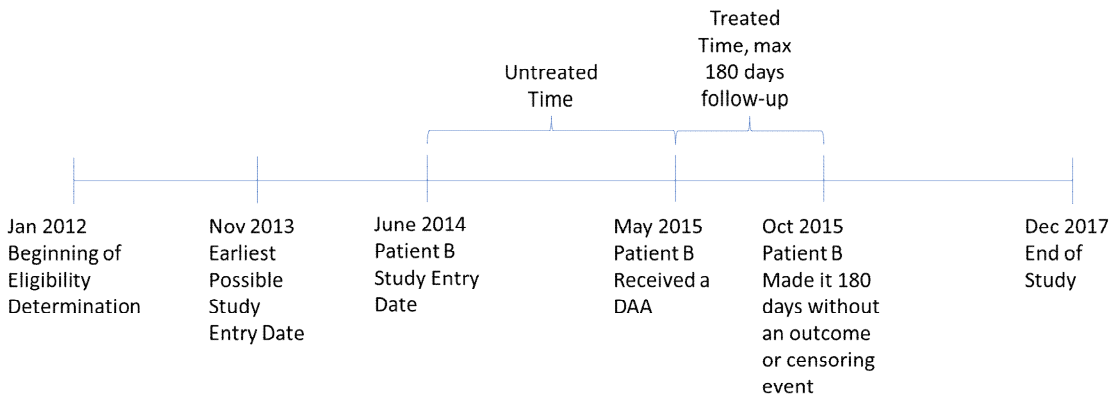
Appendix 1. Graphical Representation of Study Design with Three Examples

Patient A: No DAA received



Patient B: DAA received

Case 1: no outcome occurred



Patient B: DAA received

Case 2: Outcome or censoring event