Active surveillance and real world evidence in the evaluation of treaments in patients with chronic hepatitis C

Summary

At the time of our original grant submission, only three drug regimens were available for the treatment of the hepatitis C virus (HCV), none of which are commonly used for HCV treatment today. There are now six DAA-based regimens currently being used, with ribavirin often being included to prevent resistance and lower relapse rates of HCV, thus improving treatment effectiveness.

Consequently, patient numbers for potential recruitment were distributed across multiple therapies, with or without ribavirin, rather than the two therapies we had originally anticipated. As such, in order to adapt to the current standard of care, we had to significantly increase patient recruitment to sufficiently power necessary analyses.

Implications

We demonstrated our ability to accommodate to rapidly changing clinical practice and to ensure that our research questions remain relevant to the new standards of care. Our SEARCH surveillance team has been highly successful in responding to the rapid uptake of several new therapies by enrolling 676 patients and completing patient recruitment in 2019.

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What is the current situation?

From 2003 to 2011, chronic hepatitis C was treated with a combination of pegylated interferon and ribavirin (Peg-IFN/RBV). In 2011, the use of the direct acting antivirals (DAAs), boceprevir (Victrelis®) and telaprevir (Incivek®), became standard therapy but have have since been discontinued (telaprevir in 2015 and boceprevir in 2016) due to the development of newer DAAs. The hepatitis C virus (HCV) treatment landscape has evolved rapidly with 11 new drugs or drug combinations receiving approval between 2013 and 2018. Treatment regimens currently available in Canada include: sofosbuvir + daclatasvir (Sovaldi® + Daklinza®), ledipasvir/sofosbuvir (Harvoni®), velpatasvir/sofosbuvir (Epclusa®), elbasvir/grazoprevir (Zepatier®), glecaprevir/pibrentasvir (Maviret®), and sofosbuvir/velpatasvir/voxilaprevir (Vosevi®).

What was the aim of the study?

To examine the extent to which patient-specific genetic factors help predict the safety and effectiveness of hepatitis C treatments used to treat Canadian patients.

How was the study conducted?

There are six DAA-based regimens currently being used, **none of which were available at the time of our original grant submission.** Ribavirin is often added to treatment regimens to prevent resistance and lower relapse rates of HCV, thus improving treatment effectiveness. The use of six different regimens with or without ribavirin, meant that recruitment of patients was distributed across multiple therapies. As a result, we had to significantly increase patient recruitment to sufficiently power the necessary analyses. Using active surveillance, we tracked adverse drug reactions that were clinically relevant for Canadian patients treated with these new drug regimens. The two most clinically releveant reactions were therapeutic failure and anemia. This study allowed us to examine drug outcomes in real-world patient cohorts and compare these to drug outcomes in clinical trials.

What did the study find?

- Active surveillance is an effective method to generate real world data on drug outcomes.
- This method allowed for necessary flexibility over the study to reflect multiple, rapid changes in drug treatment regimens that were occurring in real time.
- Given that 95% of adverse drug reactions (ADRs) are not reported, and that therapeutic failure is the most common ADR, active surveillance methods enabled us to capture cases of therapeutic failure which occurred in the real world at 5 times the rate of pivotal clinical trials.
- This method allowed us to better characterize therapeutic failure with the use of sofosbuvir, often used as the backbone of current HCV therapy, as well as characterize the genetic basis of ribavirin-induced anemia.

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