Hepatitis C Treatments: Contribution of Patient Genetics in Sofosbuvir Treatment Failure

Summary

Despite low rates of sofosbuvir failure in the pivotal clinical trials (2 - 4%), this real-world trial shows a higher failure rate of 9.5%. This study also found that patients with certain genetic variants in *CES1*, which encodes an enzyme required for sofosbuvir activation, have more than five times the rate of sofosbuvir failure. Additionally, a genetic variant that increases interferon lambda signaling, which is an important part of the immune response to the virus, more than doubles the chance of sofosbuvir failure.

Implications

Based on genetics, patients who are at a high risk of sofosbuvir treatment failure can be identified before treatment begins.

The prediction of patients unlikely to respond to this costly drug, would save money and ensure such patients are placed on more effective therapy sooner, and before treatment failure occurs.

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What is the current situation?

- In Canada, 12,447 cases of hepatitis C virus (HCV) were reported in 2018, representing a rate of 33.6 per 100,000 people and an increase of 13% since 2014.
- If left untreated, hepatitis C infection can lead to liver-related complications such as liver cancer, where complications resulted in approximately 400,000 deaths worldwide in 2015.
- Sofosbuvir is considered a key drug to eradicate the virus, with cure rates approaching 100% in pivotal clinical trials, yet up to 10% of real-world patients still fail treatment.
- Treatment failure is usually assumed to be due to viral polymorphisms resistant to antiviral medications or clinical risk factors such as advanced liver disease.
- However, viral and clinical risk factors are not sufficient to predict who will fail treatment.

What was the aim of the study?

- To examine the extent to which patient-specific genetic factors help predict sofosbuvir treatment failure in Canadian patients with chronic hepatitis C.

How was the study conducted?

- Patients who received sofosbuvir-based antiviral therapy to treat hepatitis C were enrolled from adverse drug reaction surveillance sites across Canada that are part of the SEARCH & PREVENT Team of the CIHR Drug Safety and Effectiveness Network (DSEN)
- 359 patients were recruited from multiple HCV clinic sites in three provinces (British Columbia, Alberta and Ontario).
- Patient DNA samples were assessed for approximately 700,000 genetic variants across the genome, with analyses focused on patient genetic factors predicted to decrease a patient's drug exposure or modulate their immune response to viral infections.

What did the study find?

- In this real-world cohort, representing more heterogeneous patients and treatment strategies compared to clinical trials, 34/359 (**9.5%**) of sofosbuvir-treated patients experienced treatment failure v. 2 - 4% in published pivotal clinical trials.
- Patient genetic variants in *CES1*, which encodes an enzyme required for production of sofosbuvir's active metabolite, increase the rate of sofosbuvir failure more than **five times** in patients of European ancestry.
- A genetic variant that increases interferon lambda signaling through *IFNL4* activation more than **doubles** the chance of treatment failure with sofosbuvir-based regimens.
- Patient-specific genetic factors that predict sofosbuvir-based treatment failure are a **powerful tool** to guide treatment choice to ensure effective treatment.

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