Hepatitis C Virus Treatment: Contribution of Patient Genetics in Ribavirin-induced Anemia

Summary

In the treatment of chronic hepatitis C, ribavirin is often incorporated to improve treatment effectiveness. However, 1 in 3 treated patients develop severe anemia. This study found that a genetic variant in *ITPA*, which relieves oxidative stress, leads to a decreased risk of ribavirin-induced anemia. In contrast, a variant in the *VDR* gene increases oxidative stress and doubles the risk of anemia. Promising protective roles were identified for variants in *GYPC*, which is involved in red blood cell stability, and variants in *IRF7* and *RASGRP3,* which play roles in red blood cell production.

Implications

Based on genetics, patients who are at a high risk of ribavirin-induced anemia can be identified before treatment begins.

Predicting which patients are at a high risk of serious ribavirin-induced anemia before treatment enables the use of risk-based ribavirin dosing. This would improve both health and safety for the patient and the likelihood of completing successful treatments in difficult-to-treat populations.

CIHR IRSC
Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

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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 untreated, hepatitis C infection can lead to liver-related complications (e.g., liver cancer) where complications resulted in approximately 400,000 deaths worldwide in 2015.
- Ribavirin, a broad-spectrum antiviral, is added in regimens for difficult-to-treat cases to prevent resistance and lower relapse rates of HCV to improve treatment effectiveness.
- Ribavirin is also used to treat hepatitis E, paramyxovirus infections, and it is the only known or licenced treatment for Lassa fever and pediatric repiratory syncytial virus.
- Despite its clinical utility, ribavirin use is accompanied by the development of serious hemolytic anemia in 1 of 3 treated patients, which can lead to treatment discontinuation.
- Clinical risk factors are not sufficient to predict who will develop serious ribavirin-induced anemia.

What was the aim of the study?

- To examine the extent to which patient-specific genetic factors help predict ribavirin-induced anemia in Canadian patients with chronic HCV.

How was the study conducted?

- Patients who received ribavirin-containing antiviral therapy to treat hepatitis C were recruited 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)
- 235 patients were recruited from multiple HCV clinic sites in three provinces: British Columbia, Alberta and Ontario.
- Patient DNA samples, along with clinical data, were collected and tested for approximately 700,000 genetic variants across the genome for use in both candidate gene and genome-wide analyses.

What did the study find?

- This study showed that the presence of a variant in the *VDR* gene, **doubles the risk** of ribavirin-induced anemia through increasing oxidative stress.
- This study also identified genetic variants with biologically-relevant roles that approached genome-wide significance for predicting ribavirin-induced anemia. *GYPC*, influencing red blood cell (RBC) stability, is associated with an **8-fold lower** risk. *IFR7* and *RASGRP3* increase RBC production and are associated with **4-fold lower** and **3-fold lower** risks respectively.
- The presence of a variant in *ITPA* that reduces oxidative stress, leads to an **8-fold decrease** in the risk of ribavirin-induced anemia.

Lin JJ, Loucks CM, Trueman JN, Drögemöller BI, Wright GEB, Yoshida EM, Ford J, Lee SS, Kim RB, Al-Judaibi B, Schwarz UI, Ramji A, Tam E, Ross CJ, Carleton BC. Novel variant in glycophorin c gene protects against ribavirin-induced anemia during chronic hepatitis C treatment. Biomed Pharmacother. 2021 Nov;143:112195. PMID: 34562771

This research was funded by CIHR – Drug Safety and Effectiveness Network and conducted by investigators affiliated with the following institutions:

THE UNIVERSITY OF BRITISH COLUMBIA
UNIVERSITY OF CALGARY
Western
Canadian Pharmacogenomics Network for Drug Safety