Mutating hepatitis viruses make drug treatment difficult: Study highlights importance of variant profiling

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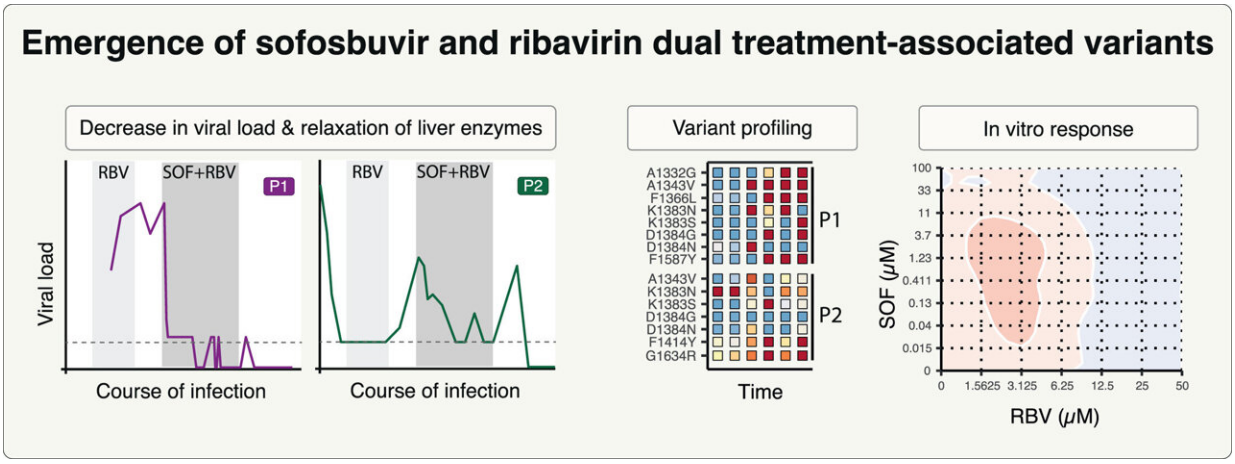

Graphical abstract. Credit: *JHEP Reports* (2024). DOI: 10.1016/j.jhepr.2023.100989

Hepatitis E affects over 20 million people worldwide. It clears up without any consequences in most cases, but it can pose a risk to pregnant women and immunocompromised patients. There are no specific active substances against the virus.

Researchers at Ruhr University Bochum and Hannover Medical School have closely monitored the evolution of the virus in two chronic patients undergoing combination therapy with the antiviral agent ribavirin and

sofosbuvir, which was developed to combat hepatitis C.

They identified variants that lead to resistance. Their findings may help to develop better active substances. The team published their findings in the journal *JHep Reports*.

The virus mutates in the body

The study team monitored two patients with chronic hepatitis E who had not previously responded to ribavirin and who were then treated with a combination of sofosbuvir and ribavirin.

"In both cases, the combination therapy was more effective than treatment with just one active ingredient," says Dr. André Gömer from the Department of Medical and Molecular Virology at Ruhr University Bochum. "In both patients, the viral RNA in the blood and stool initially dropped almost to the detection limit." This observation is in line with findings from therapy of other viral diseases such as HIV, which is also treated with combinations of individual active substances.

Study paves the way for the next generation of active substances

At a later stage, however, more hepatitis E virus (HEV) was detected again, as resistant variants emerged. Specifically, the variants called A1343V and G1634R proved to be resistant to the combination therapy.

"However, the viral load remained low in both patients and the infection healed completely in one of them over the course of several months," says Dr. Katja Dinkelborg, clinician and researcher from Hanover. "The other patient also recovered after another short course of ribavirin therapy, meaning that combination therapy with sofosbuvir should be

considered in cases of severe courses of chronic hepatitis E after failed ribavirin monotherapy."

Nonetheless, the research team points out that hepatitis E remains a serious global health problem due to a lack of specific anti-HEV drugs. "Even though drugs such as ribavirin, interferon and sofosbuvir have shown potential, the rapid emergence of resistant variants poses a considerable challenge," concludes Professor Benjamin Maasoumy, Senior Consultant at the Department of Gastroenterology, Hepatology, Infectiology and Endocrinology at Hannover Medical School.

The current study does more than highlight the effectiveness and limitations of current treatment; it also provides valuable insights into the evolutionary dynamics of HEV, paving the way for the next generation of antiviral treatments.

Hepatitis E

The hepatitis E virus (HEV) is the main cause of acute viral hepatitis. Approximately 70,000 people die from the disease every year. After the first documented epidemic outbreak between 1955 and 1956, more than 50 years passed before researchers began to explore the issue in depth.

Acute infections usually clear up spontaneously in patients with an intact immune system. In patients with a reduced or suppressed immune system, such as organ transplant recipients or people infected with HIV, HEV can become chronic. In addition, HEV poses a serious threat to pregnant women.

More information: André Gömer et al, Dynamic evolution of the sofosbuvir-associated variant A1343V in HEV-infected patients under concomitant sofosbuvir-ribavirin treatment, *JHEP Reports* (2024). DOI: 10.1016/j.jhepr.2023.100989

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