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Case report

Ledipasvir/sofosbuvir and ribavirin for the treatment of ribavirin-refractory persistent hepatitis E virus infection

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ABSTRACT

Persistent Hepatitis E Virus infection (HEV) is a rare but increasingly recognised condition in immunocompromised individuals. Untreated, this infection can rapidly progress to cirrhosis. Ribavirin is recommended as the first line treatment and the majority achieve sustained viral clearance. However, treatment options are limited for those who fail ribavirin. We report a case of a patients with ribavirin-refractory persistent HEV who responded to ledipasvir/sofosbuvir and ribavirin treatment. This patients had failed 2 course of ribavirin and 1 course of PEG-Interferon and ribavirin and he was known to harbour ribavirin-associated mutations (G1634R, D1384G and K1383N) in the RNA dependent RNA polymerase. He was treated with ledipasvir/sofosbuvir (LDV/SOF; Harvoni 90/400 mg) and ribavirin (R) 400 mg twice daily for 32 weeks. At treatment initiation his HEV RNA was 1.1×10^6 IU/ML and reduced to 1.8×10^4 IU/ML and 43 IU/ML at one and four weeks of treatment, respectively, becoming not detected in blood and stool by week eight. His blood HEV RNA remained undetectable for seven months after treatment completion. Unfortunately, at eight months post-treatment, his blood HEV RNA became detectable at a low level (35 IU/ML). His stool HEV RNA was also detectable at 620 IU/ML consistent with a late relapse. He restarted LDV/SOF+R and by week four of treatment HEV RNA was not detected in blood and stool. He remains on treatment. In conclusion, this is the first report demonstrating the antiviral activity of LDV/SOF+R in the treatment of persistent HEV infection.

Persistent Hepatitis E Virus infection (HEV) is a rare but increasingly recognised condition in immunocompromised individuals [1]. Untreated, this infection can rapidly progress to cirrhosis. Ribavirin is recommended as the first line treatment and the majority achieve sustained viral clearance [2,3]. However, treatment options are limited for those who fail ribavirin [4]. We report a case of ribavirin-refractory persistent HEV who responded to ledipasvir/sofosbuvir and ribavirin treatment.

The patient's clinical history has been previously described [5]. The patient provided consent for publication of his clinical information and review. In brief, this 82-year-old male had a history of gastric marginal zone lymphoma that was cured with chemo-radiotherapy in 2011, but he developed chronic autoimmune neutropenia. In March 2016, he was diagnosed with persistent HEV genotype 3c infection. His HEV treatment history and blood test results are summarised in Fig. 1. He was initially treated with 12-weeks of ribavirin 400 mg twice daily, but relapsed despite two sequential HEV RNA negative tests in blood and stool at week 8 and 12 of treatment. He subsequently failed to respond to six months of ribavirin 400 mg twice daily and then nine months of PEG-interferon (PEGASYS 180 mcg weekly) and ribavirin 400 mg twice daily. He developed ribavirin-associated mutations (G1634R, D1384G and K1383N) in the RNA dependent RNA polymerase during these treatments. Adherence was good. His liver stiffness measurement increased from 6 kPa in 2016–16.7 kPa in 2020 indicating he had developed advanced liver fibrosis.

Given the progression to advanced fibrosis, we explored alternative treatments including an unsuccessful attempt to treat him with convalescent plasma containing high level anti-HEV IgG [5]. Previous *in vitro* studies had shown sofosbuvir to exhibit antiviral activity against HEV and this effect was additive when combined with ribavirin [6].

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Moreover, a small human study showed that sofosbuvir monotherapy reduced HEV RNA by 1.1 $\log^{10}$ IU/ML [7]. We gained approval from our hospital drug and therapeutics committee to treat with sofosbuvir and ribavirin. However, due to local drug availability he was treated with ledipasvir/sofosbuvir (Harvoni; 90/400 mg) and ribavirin 400 mg twice daily (LDV/SOF+R).

At treatment initiation his blood tests were as follows: plasma HEV RNA 1.1×10^6 IU/ML, ALT 277 U/L (normal range <40 U/L), ALP 974 U/L (normal range <130 U/L) and total bilirubin 34 umol/L (normal range <20 umol/L). Viral sequencing showed the G1634R and D1834G mutations persisted and V1305I appeared. He had lost the K1383N variant. The HEV RNA reduced to 1.8×10^4 IU/ML and 43 IU/ML at one and four weeks of treatment, respectively, becoming not detected in blood and stool by week eight. At week one of treatment the G1634R, D1834G and V1305I mutations persisted. He was treated for 32 weeks and HEV RNA remained not detected in blood and stool. At the end of treatment his liver enzymes had improved (ALT 26 U/L, ALP 674 U/L and Bilirubin 11 umol/L). His blood HEV RNA remained undetectable for seven months after treatment completion. Unfortunately, at eight months post-treatment, his blood HEV RNA became detectable at a low level (35 IU/ML). His stool HEV RNA was also detectable at 620 IU/ML consistent with a late relapse. He restarted LDV/SOF+R and by week four of treatment HEV RNA was not detected in blood and stool. He remains on treatment with a plan to treat for four months. The patient was reluctant to have a more prolonged treatment due to symptoms of anaemia secondary to ribavirin.

Ribavirin-refractory persistent HEV infection is being increasingly recognised [4], and treatment options are limited. We elected to treat our patient with LDV/SOF+R to reduce the risk of liver disease progression. The observed response was remarkable with HEV RNA becoming undetectable at week eight of treatment and remained so for seven months post-treatment completion. It is known that both ribavirin and sofosbuvir have antiviral activity against HEV [6,7], but ledipasvir has not been studied. In the context of this one case, we cannot comment whether the observed favourable response was related to the combination of ribavirin and sofosbuvir or the addition of ledipasvir. There have been previous reports of a partial antiviral response during treatment with sofosbuvir and ribavirin but clearance of HEV was not achieved [8,9]. Given our observation, studies assessing the anti-HEV activity of ledipasvir alone and in combination with sofosbuvir and ribavirin are warranted.

Our patient had a late relapse eight months after apparent clearance of HEV infection. This observation raises the importance of long-term monitoring for relapse in patients with persistent HEV who achieve viral clearance with treatment. Previous work in a swine model indicated that HEV replicates in extrahepatic sites including intestines, lymph nodes and tonsils [10]. These areas could act as sanctuary sites for HEV during antiviral treatment, potentially predisposing patients to relapse.

In conclusion, this is the first report demonstrating the efficacy of LDV/SOF+R in the treatment of persistent HEV infection.

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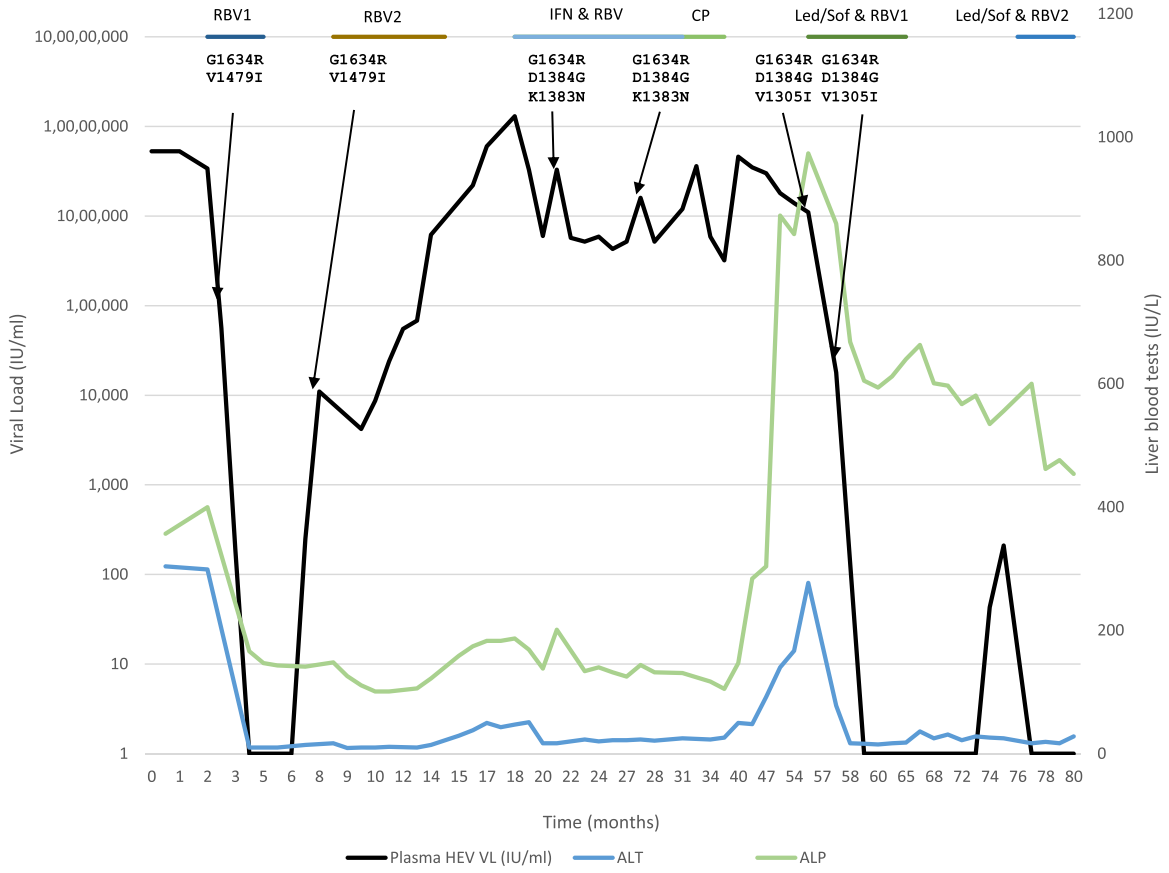

Fig. 1. HEV treatment history and blood results. This shows clinical course of blood results including the plasma HEV RNA viral load, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP). Viral sequencing results for mutations associated with ribavirin failure are also shown throughout the clinical course. CP: convalescent plasma.

Ethical approval

Informed consent obtained from the patient.

Consent

Obtained from patient.

CRediT authorship contribution statement

JG and SM managed the patient and wrote the first draft of the manuscript. YT, SI AF conducted and interpreted the laboratory tests and virus sequencing, and revised the manuscript. All authors approved the final version of the manuscript.

Conflict of interest statement

SM has received fees for lectures and consultancy and research funding from Gilead outside the submitted work. The other authors has nothing to declare.

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