LETTER TO THE EDITORS

HCV and HEV recurrence after liver transplantation: one antiviral therapy for two viruses

Eleonora De Martin[1,2,3,4], Teresa M. Antonini[1,2,3,4], Audrey Coilly[1,2,3,4], Gabriella Pittau[1,2,3,4], Eric Vibert[1,2,3,4], Jean-Charles Duclos-Vallée[1,2,3,4], Didier Samuel[1,2,3,4] & Anne-Marie Roque-Afonso[2,3,4,5]

1 Centre Hépato-Biliaire, AP-HP Hôpital Paul-Brousse, Villejuif, France
2 Inserm, UMR-S 1193, Université Paris-Saclay, Villejuif, France
3 Univ Paris-Sud, UMR-S 1193, Université Paris-Saclay, Villejuif, France
4 DHU Hepatinov, Villejuif, France
5 Service de Virologie, AP-HP Hôpital Paul-Brousse, Villejuif, France
E-mail: eleonora.demartin@aphp.fr

Dear Editors,

In liver transplantation (LT) recipients, the prevalence of Hepatitis E Virus (HEV)-RNA is about 1–3%, possibly leading to cirrhosis within 1–2 years [1]. Seroprevalence, without viremic infection, is highly variable, reported up to 42% in US patients treated for Hepatitis C Virus (HCV) recurrence after LT [2].

We report for the first time the concomitant recurrence of HCV and HEV after LT.

A 56-year-old man underwent LT for HCV, genotype (G) 1a, treatment-naïve cirrhosis. He was retransplanted 6 months later for chronic rejection. Immunosuppression combined tacrolimus, mycophenolate mofetil and steroids. Two months after re-LT, transaminases raised (ALT 1493 IU/l). Tacrolimus trough level was between 6 and 8 ng/ml. HCV viral load was 6.84 $\log_{10}$ IU/ml, and HCV recurrence was histologically proved. A systematic HEV-RNA screening detected an HEV G3e infection with a viral load of 5.82 $\log_{10}$ IU/ml. IgM and IgG were negative. Retrospectively HEV-RNA was detectable from 3 months after the first LT. Both blood products and liver tissue of the first donor were negative. A food-borne contamination was likely. Antiviral therapy combining sofosbuvir (SOF) (400 mg/day), daclatasvir (DCV) (60 mg/day) and ribavirin (RBV) (1000 mg/day) was initiated for 24 weeks. This combination was the only available. At baseline, biology showed: Hb 13.6 g/dl, creatinine 150 μmol/l, ALT 437 IU/l. Anaemia rapidly occurred, requiring RBV dose reduction, blood transfusions and erythropoietin administration. RBV serum concentration at week (W) 12 was 4633 ng/ml with therapeutic limit of 2200 ng/ml. RBV was further decreased to 200 ng/day. Regarding HCV, the viral load was undetectable from W6 and the patient achieved a sustained virological response after W12 of treatment discontinuation (SVR12). HEV PCR had flare-up at W8 (Fig. 1), but was undetectable from W12. The G1634R mutation in the RNA-dependent RNA polymerase region of HEV was detected in the baseline serum. In this context, RBV was maintained for 8 W after SOF/DCV discontinuation. No resistance tests were performed for HCV.

First, the extensive investigation we performed retrospectively, looking for the route of HEV transmission, leads to diagnosis of viral recurrence rather than *primo* infection.

Second, HCV and HEV can simultaneously recur after LT as demonstrated by our work-up. The HEV diagnosis cannot be made on liver biopsy, due to the prevalence of HCV histological features; thus, HEV needs to be systematically tested in case of increase in transaminases. Moreover, since serology is not sensitive enough [1], HEV PCR should be always tested.

Third, a three-month course of RBV remains the recommended treatment for chronic HEV infection, with a SVR of 78% [3]. Dao Thi *et al.* [4] showed that SOF inhibited HEV-RNA replication in vitro and had an additive effect with RBV, but these findings need to be clinically validated. Therefore, the choice of HCV antiviral therapy for a patient with concomitant HEV infection should be RBV based.

The HEV flare prompted us to seek HEV-RNA mutation. Interestingly, G1634R mutation in the RNA-dependent RNA polymerase region of HEV appears to increase the replicative capacity of HEV in the human liver [5]. The prolonged RBV therapy might have covered the replication fitness induced by the mutation; however, the benefit of an extended treatment is not demonstrated.

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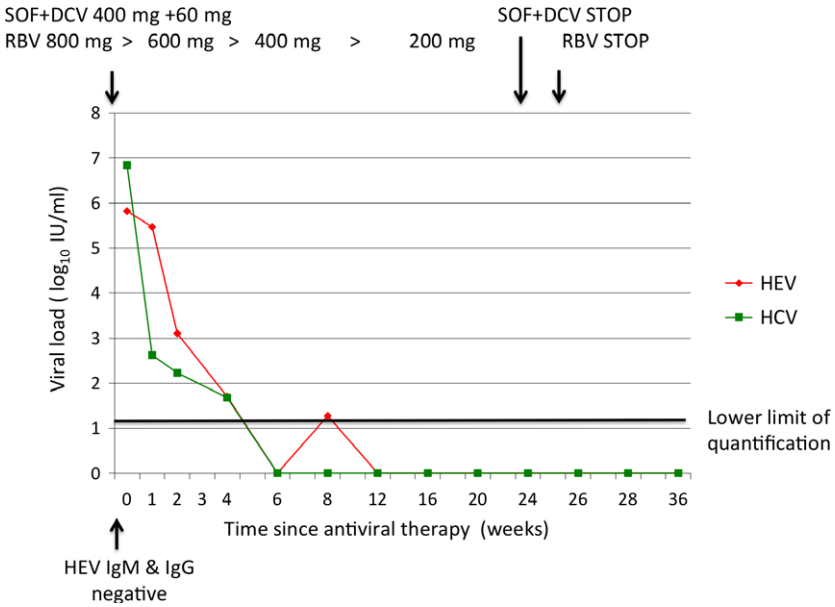

Figure 1 Evolution of HCV-RNA and HEV-RNA levels during and after antiviral therapy. Correlation with ribavirin (RBV) changes.

In conclusion, HEV and HCV can recur simultaneously after LT, viral load research is mandatory and antiviral therapy should target both viruses.

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