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Letter to the Editor

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Hepatitis C RNA clearance after treatment with ezetimibe

To the Editor:

It has been shown that hepatitis C virus (HCV) is highly dependent on lipid metabolism, exploiting the host processes of cholesterol entry (1) and intracellular trafficking (2). The recent description of Niemann-Pick C1-like 1 (NPC1L1) protein as an entry factor for HCV to host cells (3), prompted us to report the following observation: A 57-year-old female Hispanic patient presented with a history of severe von Willebrand's disease, with multiple transfusions during her infancy and genotype 1b chronic hepatitis C diagnosed in 1990. She was treated with regular interferon in 1992 for 6 months with no biochemical response. A second course of treatment with interferon alfa 2b 3 million units 3 times per week plus ribavirin 1000 mg QD was attempted in 1999. The patient developed diarrhoea, depression and skin rash, tolerating only 24 weeks of treatment. A third treatment was attempted in 2004 with peginterferon alfa 2a 180 mcg per week plus ribavirin 1000 mg QD (Fig. 1). The patient developed fatigue and skin rash, so peginterferon was reduced to 135 mcg and ribavirin to 800 mg at week 17, and ribavirin was again reduced to 400 mg at week 38. The patient completed 44 weeks of treatment. A qualitative PCR at that time was positive, confirming virological breakthrough, which coincided with an elevated alanine aminotransferase (ALT) level. Three months after stopping treatment, the patient was started on a combination of ezetimibe 10 mg plus simvastatin 10 mg QD. Her cholesterol levels (which did not change significantly before and after interferon treatment) were: total cholesterol 242, LDL 150, HDL 72 mg/dl. Three months afterwards, cholesterol levels were 152, 57 and 84 respectively. One year after stopping treatment, viral load was undetectable, and ALT normalized completely (22 U/L). Ezetimibe was given for 1 year. The HCV RNA has been persistently undetectable and aminotransferases in the normal range since then, with 6 years of follow up.

Breakthrough or relapse after treatment is not surprising for a patient infected with genotype 1b HCV and poor tolerance to interferon and ribavirin, requiring dose reductions and shortening of treatment duration. The notable point here is that HCV RNA became and remained undetectable after starting a combination of ezetimibe and simvastatin. It could be argued that the positive HCV RNA at the end of the third treatment was a false positive, but the positive correlation between ALT level and RNA detection makes this possibility less likely. Ezetimibe, a NPC1L1 antagonist, has been shown to inhibit HCV entry in cell culture and to delay infection in the humanized uPA-SCID

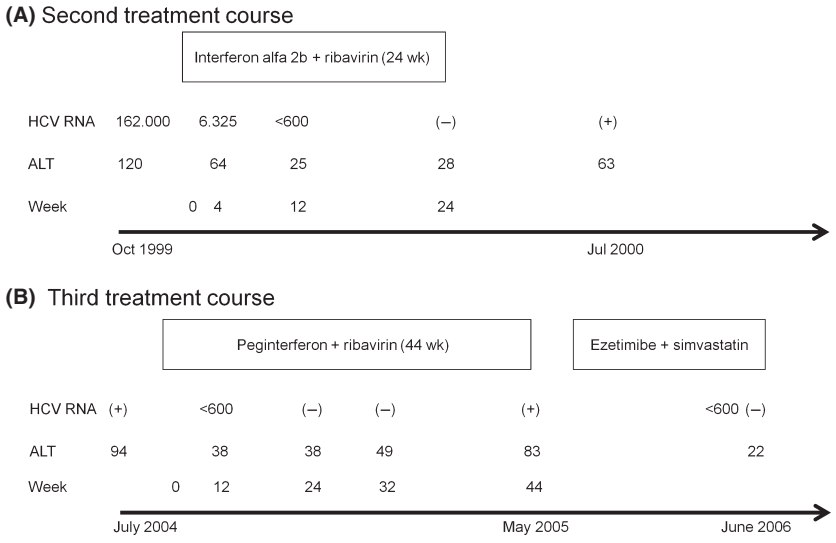

Fig. 1. Schematic diagram of treatment evolution. HCV RNA is expressed in IU/ml. HCV RNA qualitative PCR result (with a lower limit of detection of 50 IU/ml) is expressed as positive (+) or negative (–). ALT is expressed in U/L. (A) Second treatment course. (B) Third treatment course.

mice model (3) and could have decreased re-infection of hepatocytes after interferon treatment in this case. The patient received ezetimibe in combination with simvastatin. Simvastatin, despite having shown good *in vitro* activity, has failed to demonstrate any antiviral effectivity in humans (4). It is unlikely that ezetimibe treatment could cure an established infection, but it could be useful as an addition to current treatments, decreasing relapse or after liver transplantation to avoid re-infection. We do not advise treating HCV infection with ezetimibe, but this case provides anecdotal evidence supporting the design of clinical trials of ezetimibe in hepatitis C.

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