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LETTERS TO THE EDITOR

Hepatitis C virus RNA kinetics: Drug efficacy and the rate of HCV-infected cells loss

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TO THE EDITOR

We read the study by Medeiros-Filho *et al*[1] with much interest. The study shed light on early HCV RNA kinetics in conjunction with liver cirrhosis, different genotypes (gen-1 *vs* gen-3) of HCV and sustained viral response (SVR) rates. In particular, Medeiros-Filho *et al*[1] showed that the HCV RNA first phase decline, under interferon-α (IFN) and ribavirin therapy, which represents the effectiveness (ε) of IFN to block viral production[2,3], was significantly larger in gen-3 cirrhotic patients (mean $\varepsilon = 0.99$) than gen-1 cirrhotic patients (mean $\varepsilon = 0.8$). In addition, in these cirrhotic patients, they found that the HCV RNA second phase decay slope in gen-3 patients was significantly faster than in gen-1 patients, and suggested that the immune response against infected HCV cells in gen-1 patients may be less potent than in gen-3 patients.

We recently introduced the notion of a critical drug efficacy ε_c, such that if the drug efficacy, ε, is higher than the critical drug efficacy, i.e., $\varepsilon > \varepsilon_c$, then viral levels will continually decline on therapy, while if $\varepsilon < \varepsilon_c$, then viral loads will initially decline but ultimately stabilize at a steady state level lower than baseline (i.e., exhibit a flat phase)[4,5]. We have shown that the flat phase may be a simple consequence of liver homeostasis in which proliferation of hepatocytes compensates for the loss of infected cells, hence observing a flat phase does not imply a poor or absent immune response.

In light of these predictions, the interpretation of Medeiros-Filho *et al*[1] on the difference in viral kinetics between gen-1 and gen-3 in cirrhotic patients needs to be further addressed. First, if $\varepsilon < \varepsilon_c$, then following the first phase viral decay, the virus will reach a steady state lower than its baseline viral load very rapidly (i.e., flat phase). However, if ε is close to ε_c (but still $\varepsilon < \varepsilon_c$), then after the rapid viral decay phase a second slower phase of decay is predicted followed by a flat phase. Since in Medeiros-Filho *et al*[1] data was obtained only until d28 one can speculate that the drug efficacy in gen-1 cirrhotic patients, which are known to be difficult to treat, was lower than the critical drug efficacy ($\varepsilon < \varepsilon_c$) and that the 2nd slower phase reflects the flat phase or is just intermediate in an approach to reach a flat phase. Indeed, 4 of 7 gen-1 cirrhotic patients had a second phase slope equal to 0, which represents a flat phase, where the rest had a positive second phase decline slope but one that was lower than the predictive cut-off slope of SVR (i.e., 0.3 log IU/mL per week[1]), that may indicate an intermediate in an approach to reach the aforementioned flat phase.

Second, if $\varepsilon > \varepsilon_c$, then the viral second phase slope represents the death/loss rate of HCV-infected cells only if $\varepsilon \sim 1$[4,5]. Thus, if ε in some gen-1 cirrhotic patients from Medeiros-Filho *et al*[1] was higher then ε_c, then the 2nd slope decay still does not reflect with confidence the actual death/loss rate of HCV-infected cells, since the IFN effectiveness, ε, was < 1 (mean $\varepsilon = 0.8$). However, in gen-3 cirrhotic patients for which the mean value of the IFN effectiveness was close to 1 (mean $\varepsilon = 0.99$), the second phase slope could well reflect the immune-mediated loss rate of HCV-infected cells. Thus, we argue that the mechanisms that lead to different viral kinetics between gen-1 and gen-3 cirrhotic patients may be attributed to different drug effectivenesses and not solely to the immune response against HCV-infected cells.

In conclusion, Medeiros-Filho *et al*[1] made an important step towards understanding why cirrhotic patients have lower SVR rates (see also review on therapy in HCV decompensated cirrhotic patients by Navasa & Forns[6]). However, we suggest that in future studies data sampling longer than d28 needs to be done in order to better capture the viral kinetic profiles in treated cirrhotic patients.

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