LETTER

Reply to Guedj et al.: Early transient increase of hepatitis C virus viral load in genotype 1 and 2 infections, and the use of mathematical modeling

We appreciate the comments of Guedj et al. (1) on our paper addressing the association of IL28B gene variations with mathematical modeling of viral kinetics in patients with chronic hepatitis C treated with pegylated IFN plus ribavirin therapy (2). Regarding the distribution of the blips among hepatitis C virus (HCV) genotypes, we not only found a lower virion production rate but earlier blips among patients with HCV genotype 2 infection than those with genotype 1 infection. The time for the observed maximal viral load and the estimated time for maximal viral load were significantly different between these two genotypes (genotype 1 vs. 2: 0.33 ± 0.35 vs. 0.19 ± 0.12; $P = 0.0048$ and $P = 0.0106$ for the t test and Wilcoxon test), and the time for the maximal value also showed that patients with HCV genotype 1 infection had a poorer virological response than those with genotype 2 infection (Table 1). However, as reported in our paper, although HCV genotype has long been known as a predictor of achieving sustained virological response (SVR) in patients treated with combination therapy, it also serves as a latent factor of viral kinetics, especially for virion production rate. Thus, the impact of HCV genotype on SVR was not significant in our regression models, and viral kinetic parameters were still better than HCV genotype in the prediction of SVR.

As to the modeling of HCV kinetics during combination therapy, we assumed that target cells remained constant in the first 2 wk and estimated K_1' and K_2' by fitting the viral load data of the first 3 d for each patient. Because all patients had persistent HCV infection, their viral loads would be in the steady state (a state of equilibrium), almost remain constant before therapy, and not increase before therapy, as raised by Guedj et al. (1). However, this does not indicate that the viral loads will surely decline after treatment because there could be a transition state in the very early stage of therapy. Thus, we chose the solution (three-parameter solution) that could model the observed earlier blips of the earlier transition state. The earlier transition state corresponds to the condition $\delta = c$, which is necessary for the three-parameter solution to hold. In other words, we have a state of equilibrium, $\delta = c$, in the earlier transition state. On the other hand, the four-parameter solution, the choice of the standard mathematical model for HCV infection and treatment (3), represents the other state of "equilibrium." According to this standard model, "c is approximately 50 times larger than δ" (4), and we believe that the patients with this kind of condition are not analyzed under the consideration of earlier transition state but are only focused on in the state of viral load progression before SVR and that this later equilibrium is achieved under the complex interactions of therapy, the host immune system, and HCV from the earlier transition state.

Table 1. Time of transient HCV titer elevation in patients with genotype 1 or 2 infection

Day to maximal viral load	Genotype = 1	Genotype = 2
0.33	16	15
0.5	13	13
0.67	21	5
1	2	1
1.5	2	1
2	0	0
3	0	1

Data are shown by case number. Patients with transiently elevated HCV titers were those whose HCV titers during the first 3 d of treatment were higher than baseline titers, and 90 patients had transient elevated HCV titers before the decline of viral load.

Therefore, our three-parameter model and the standard model indeed present different equilibrium states of HCV kinetics. Further modeling of the "changes" between these two different equilibrium states is essential to understand the interactions and will be the key to unravel the whole picture of HCV kinetics.

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The authors declare no conflict of interest.

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