Clinical relevance of detectable HCV RNA in the context of Direct-Acting Antivirals

To the Editor:

Harrington et al. discuss the clinical relevance of detectable, but not quantifiable, hepatitis C viral (HCV) RNA during treatment with the two recently approved direct-acting antivirals (DAAs), boceprevir and telaprevir.[1] The clinical trials used to assess the efficacy of these new DAAs were not designed to assess response-guided therapy using the less than lower limit of quantification [LLOQ] cutoff. However, a viremia below the LLOQ, but with detectable amounts of virus, clearly indicates that peripheral clearance has not occurred and, by implication, that replicating virus is still present in the liver. The endpoint for the LLOQ for most clinical trials is 25 IU/mL (1.39 $\log_{10}$). The reduction in the sustained virological response (SVR) rate between those patients that have a viremia less than the LLOQ and those that have no detectable viremia clearly indicates that lack of peripheral suppression is still a good surrogate for persistence. No assay currently available detects HCV down to a level of 0.001 IU/mL, as outlined in Figure 1 of Harrington et al.[1]

We have assessed the decreasing confidence interval (CI) associated with HCV reverse-transcriptase polymerase chain reaction (RT-PCR) on a panel of characterized HCV genotype 1b samples (100, 37, 10, 3.7, 1, 0.37, and 0.04 IU/mL; AcroMetrix; Invitrogen, Carlsbad, CA). The test platform was the Roche AmpliPrep and TaqMan 48 (Roche Molecular Diagnostics, Pleasanton, CA). Tests were replicated between 13 and 25 times. A 100% hit rate was achieved for the 100- and 37-IU/mL samples. A 95% CI was achieved at 9.914 (range, 5.737-26.578; n = 13). Probit analysis yielded a 60% hit rate at 2.624 IU/mL (95% CI: 1.782-4.241) and a 40% hit rate at 1.564 IU/mL (95% CI: 1.011-2.322). The assay did not yield detectable RNA for the 0.37- and 0.04-titer samples (n = 25 and n = 18, respectively). We agree with Harrington et al.'s suggestion that validated cut-off LLOD points with appropriate CIs are applicable to the provision of optimal care and maximizing of SVR rates. An understanding of the decline in CIs surely makes the assessment of end-of-treatment detectable (but below the LLOQ) results as false positives too convenient an explanation. [1] These transient viremias may be somewhat inconvenient to explain, but perhaps our understanding of the natural history of HCV infection in the context of DAAs is insufficient to simply overlook the possibility that these transient viremias represent detectable, real virus.

It is important that we are mindful of the caveats associated with any molecular platform and that any detectable viremia, in the context of DAA therapy, indicates, primarily, incomplete clearance of the virus from the target organ and, secondarily, that the nonrepeatable positive may be a casualty of decreasing CIs, rather than a false positive.

1. Harrington PR, Zeng W, Naeger LK. Clinical relevance of detectable but not quantifiable hepatitis C virus RNA during boceprevir or telaprevir treatment. HEPATOLOGY 2012;55:1048-1057.

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