Two Years’ Persistence of Naturally Present Substitution R155K Within Hepatitis C Virus NS3 Protease in the Absence of Protease Inhibitor–based Therapy

To the Editor—Kim et al recently published an interesting study about temporal dynamics within hepatitis C virus (HCV) NS3 protease of amino acid substitution R155K, which confers resistance to specific HCV protease inhibitors (PIs) [1]. They described, in a patient never exposed to PI, the stability of naturally present R155K variants as the predominant strains during 37 weeks, then their detection as mixtures concurrently with wild-type viruses until week 64 and their absence when tested nearly 5 years later. We report here the persistence, in the absence of PI therapy, of naturally present R155K-HCV (Genbank accession no. HQ149068–HQ149081) as the only detectable strains during a 113-week period. The patient is a 41-year-old HIV-seronegative man with HCV-related decompensated liver cirrhosis diagnosed in February 2007, and in whom we previously detected the natural presence of R155K-HCV genotype 1a [2]. The patient received a liver transplant in August 2007 and experienced HCV recurrence 1 month later (Figure 1). Later on, he received pegylated interferon-α and ribavirin from June 2008 to October 2009. HCV RNA never became undetectable; in addition, virologic escape occurred and HCV load increased to pretreatment level after therapy interruption (Figure 1). Throughout the entire follow-up, amino acid 155K was detected by means of population sequencing from 5 serum samples and was harbored by 9 of 9 clonal sequences as assessed on the last sample (Figure 1).

Naturally occurring R155K-HCV have been identified in <1% of HCV-infected patients [3, 4], and in 2 (4.4%) of 37 patients co-infected with HIV-1 under antiretroviral therapy including PIs [5]. So far, such viruses all belonged to genotype 1a, which has a lower genetic barrier to substitution R155K [2, 6]. R155K HCV has been shown in vitro to have impaired fitness compared with wild-type strains in the absence of drug [6]. Notwithstanding, they represented one of the fittest mutants among those emerging during PI-based therapies [6, 7]. In vivo, the coexistence in Kim et al’s study of naturally present R155K variants and of wild-type HCV over ≥1 year [1] suggests limited difference in fitness between these 2 populations, although in another study R155K-HCV were replaced by wild-type viruses in 1 patient on standard of care therapy [3]. Additionally, in the present case, R155K-HCV still persisted 113 weeks after first observation. In addition, PI-selected R155K viruses remained detectable in patients 3–7 months after treatment discontinuation [6]. Moreover, HCV RNA levels in patients infected with predominant naturally present R155K variants were >5.7 log IU/mL in 8 of 9 cases reported previously, and in the present work [1, 3, 4]. Taken together, previous findings indicate that naturally present R155K-HCV may not display clinically significantly reduced fitness compared with wild-type strains in the absence of NS3 PI-selective pressure.

No compensatory mutation was identified in our study or in previous reports of natural R155K-HCV [1, 3, 4]. However, in our case, amino acid 54S, recently associated with PI resistance [4, 8] and detected as a natural polymorphism with a frequency <1% [9], was harbored by all HCV RNA recovered in sequential serum samples. This should be emphasized because it was observed that relative fitness on therapy of HCV harboring a PI-resistant mutation could be improved if the viruses carried a second resistance mutation [6, 8]. In Kim et al’s study and in our case, it can be hypothesized that R155K-HCV persistence might have been favored by severe immunodeficiency. Indeed, in Kim et al’s report, the patient was infected with HIV-1, and his lymphocyte CD4 T cell count was 62/mm³ at the beginning of follow-up; of note, wild-type HCV emerged after CD4 count increased from 62 to 303 cells/mm³ [1]. In our case, the patient is a liver transplant recipient. In contrast to Kim et al, we did not detect wild-type HCV at position 155 of NS3 protease in sequential serum samples collected during follow-up, including in clonal sequences [2]. Liver transplantation may have led to decreased HCV quasi-species diversity, being possibly responsible for a bottleneck effect due to implantation of a new liver combined with reduced immunologic selective pressure [10, 11]. The absence or the very minority presence of wild-type strains being able to compete with R155K quasi-species may be another reason for the persistence of the latter. Thus, in the setting of HIV infection, persistence of multidrug-resistant HIV-1 without antiretroviral treatment was documented in 2 patients 2 years after sexual transmission, and clonal sequencing revealed that only multidrug-resistant viruses were detected in the source patients and could be transmitted to the index patients [12].
In conclusion, although uncommon, naturally present R155K-HCV can persist during several months, at least in severely immunocompromised persons, and may jeopardize the efficacy of PI-based therapies [3].

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