Practical Consequences of Hepatitis C Virus Quasispecies for Target-Specific Antivirals

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(See the article by Bartels et al., on pages 800–7.)

Hepatitis C virus (HCV) exists as a swarm of similar but not identical isolates, called a “quasispecies” [1, 2]. Quasispecies provide the viral population with an innate capacity to evade endogenous and exogenous challenges [3]. The study of quasispecies heterogeneity provides information on how HCV behaves as an evolving entity in response to innate and adaptive immune pressure [4–6]. In practical terms, this heterogeneity is generated by the HCV replicase, NS5B, which lacks a proofreading biofunction [7, 8]. In addition, each host places constraints on HCV genomic evolution, and these constraints can select for mutant genomes with particular molecular signatures, that is, signatures for cytotoxic T lymphocyte (CTL) escape. CTL escape occurs during many viral infections, including those caused by simian immunodeficiency virus, HIV, and HCV [9–11]. Each mutation carries a potential fitness cost for the virus, the value of which depends on the immune potency of the recipient host. Reversion in the absence of direct HLA-based selection has been shown for HCV [10]. The phenomenon of nucleotide reversion is likely due, in part, to an enhanced fitness of the revertant virus in the new host. The goal of highly active antiretroviral therapy in HIV disease is the suppression of viral replication. However, it would appear that elimination, rather than mere suppression, of viral replication in HCV disease is possible, at least in a percentage of patients [12, 13].

The current development of specific HCV inhibitors raises the very important issue of resistant viruses either existing before treatment or emerging during therapy [14–16]. Selection of resistant mutants is predictable, because viruses such as HCV exhibit natural genomic heterogeneity [2, 6, 8, 16, 17]. Preventive approaches based on the use of potent combination therapies aimed at a multitude of viral targets will likely be needed as an adjunct to the current combination of peginterferon and ribavirin [15]. The lessons learned with monotherapy and ineffective combination therapy for hepatitis B virus (HBV) and HIV infections should guide the use of antiviral agents against HCV [18, 19]. In this issue of the Journal, Bartels et al. [20] present evidence that the quasispecies phenomenon is likely responsible for the lack of efficacy of target NS3·4A protease inhibitors, such as telaprevir (VX-950). A near-full-length replicon of 9 kb (H77; nt 286–9277) was used as the source material for the investigation of the mutant spectrum in 570 of 573 treatment-naive subjects who had chronic genotype 1 HCV infection. In 0.9% of the subjects, the V36M variant was predominant. Replicon and purified-protein experiments have shown that V36M is associated with low-level resistance to telaprevir [21]. The data presented by Bartels et al. suggest that the V36M variant may have a resistance profile similar to that of wild-type virus. The R155K mutant was predominant in 0.7% of the subjects. This mutation is known to confer high levels of resistance to BILN 2061 and another macrocyclic protease inhibitor, ITMN-191, in addition to being present in patients treated with telaprevir monotherapy [15]. The prevalence of these background mutants is low but, importantly, provides further evidence for the existence of potential antiviral resistance mutants in the HCV quasispecies of untreated patients. This situation is similar to the natural occurrence of drug-resistant virions in treatment-naive HIV-infected patients [22].

The triple therapy of peginterferon, ribavirin, and telaprevir would appear to be a potent regimen, perhaps more so than standard combination therapy for this group of patients. However, subjects with the R155K variant appeared to have a slower viral load decline than patients with wild-type virus or the V36 variant. The basis for this finding is currently unclear, given that the in vitro sensitivity of
the V36M and R155K mutants to telaprevir is similar. However, the findings of Bartels et al. likely reflect differences between replicon-based investigations and the dynamic in vivo situation in the infected liver. Although the number of treated patients in this study is small, the fact that all patients with the V36M and R109K mutants who were treated with the triple therapy achieved a sustained virological response is significant.

Quasispecies are not fixed with respect to their composite virions and appear to vary by infection site [2, 10]. Genetic drift may increase over time, and successive shifts in a quasispecies will likely “purify” large numbers of variants from the periphery and, presumably, the liver. This temporal movement of quasispecies presents a difficult challenge with respect to the definition of background mutants likely to have non–wild-type sensitivity to novel antiviral agents. When would be the optimal time to initiate treatment with these new protease and polymerase inhibitors? Do windows of enhanced treatment efficacy exist during which each chronically infected patient will be more likely to respond to potentially toxic and mood-altering medications? Only prospective mapping of temporal changes to the HCV quasispecies will address these questions satisfactorily. Variances in estimating quasispecies complexity can be influenced by technical limitations and methodological bias [23, 24]. Perhaps the emerging methodology of pyrosequencing will assist in establishing the spectrum of quasispecies mutants more precisely at a time before the initiation of antiviral therapy [25, 26]. Does virus present in the periphery represent an optimal sample to determine the existence of non–wild-type virions, and does the phenomenon of archiving of quasispecies play a significant role in the reemergence of variants in HCV infections, as it does for HIV and HBV [2, 14]? Will some treatment-naive patients have mutations fixed in the viral genome that preclude the use of entire classes of drugs? These questions can best be answered by prospective investigation of the quasispecies composition of large patient cohorts. However, the study by Bartels et al. indicates that it is likely that paradigms for treatment will soon have to take into account genetic drift within those regions of the HCV genome targeted by novel antivirals. Although not the first description of the preexistence of mutant genomes likely to be resistant to target-specific antivirals, the study takes a significant step forward in HCV pharmacogenomics, estimating the likely prevalence and sensitivity of non–wild-type virions to specific antivirals that target the NS3-4A protease [14]. The phenomenon of quasispecies diversity presents interesting challenges for the future development of pan-genotype antiviral therapies.

References


