Naturally Occurring Resistance-Associated Variants of Hepatitis C Virus Protease Inhibitors in Poor Responders to Pegylated Interferon-Ribavirin

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Résumé en anglais	The pretherapeutic presence of protease inhibitor (PI) resistance-associated variants (RAVs) has not been shown to be predictive of triple-therapy outcomes in treatment-naive patients. However, they may influence the outcome in patients with less effective pegylated interferon (pegIFN)-ribavirin (RBV) backbones. Using hepatitis C virus (HCV) population sequence analysis, we retrospectively investigated the prevalence of baseline nonstructural 3 (NS3) RAVs in a multicenter cohort of poor IFN-RBV responders (i.e., prior null responders or patients with a viral load decrease of <1 log IU/ml during the pegIFN-RBV lead-in phase). The impact of the presence of these RAVs on the outcome of triple therapy was studied. Among 282 patients, the prevalances (95% confidence intervals) of baseline RAVs ranged from 5.7% (3.3% to 9.0%) to 22.0% (17.3% to 27.3%), depending to the algorithm used. Among mutations conferring a >3-fold shift in 50% inhibitory concentration (IC50) for telaprevir or boceprevir, T54S was the most frequently detected mutation (3.9%), followed by A156T, R155K (0.7%), V36M, and V55A (0.35%). Mutations were more frequently found in patients infected with genotype 1a (7.5 to 23.6%) than 1b (3.3 to 19.8%) (P = 0.03). No other sociodemographic or viroclinical characteristic was significantly associated with a higher prevalence of RAVs. No obvious effect of baseline RAVs on viral load was observed. In this cohort of poor responders to IFN-RBV, no link was found with a sustained virological response to triple therapy, regardless of the algorithm used for the detection of mutations. Based on a cross-study comparison, baseline RAVs are not more frequent in poor IFN-RBV responders than in treatment-naive patients and, even in these difficult-to-treat patients, this study demonstrates no impact on treatment outcome, arguing against resistance analysis prior to treatment.
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