CLINICAL IMPACT OF RESISTANCE-ASSOCIATED NS3/4A AND NS5A VARIANTS IN HEPATITIS C

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Due to high rates of viral replication and an error prone HCV RNA polymerase, tremendous variability of HCV has been observed within infected patients (quasispecies) with all single mutations in the entire HCV genome thought to be pre-existing. Similarly, NS3/4A and NS5A RAVs are observed at baseline in patients infected with chronic HCV. The prevalence of baseline NS5A RAVs has been reported to be 6% to 16% using population sequencing (cut off 15-25%) or deep sequencing (cut off 1%), respectively. Interestingly, the prevalence and type of baseline NS5A RAVs may vary by geographic regions. For example, the prevalence of the NS5A M28V in genotype 1a-infected patients was shown to be higher in the United States compared to Europe, 7% versus 0%, respectively. Furthermore, the prevalence of genotype 3 NS5A Y93H varied between 0% and 17% in different geographic regions. A comparison of baseline prevalence of RAVs in Japanese and Western patients showed that the prevalence of Q80L and S122G in NS3, and L28M, R30Q and Y93H in NS5A was significantly higher in Japanese patients than the Western counterparts. Many currently approved interferon (IFN)-free regimens for the treatment of chronic hepatitis C (HCV) include an inhibitor of HCV NS5A. To date, there are four NS5A inhibitors approved for treatment of chronic HCV infection; ledipasvir (LDV), daclatasvir, ombitasvir, and elbasvir. The presence of baseline NS5A RAVs may impact treatment outcome of some NS5A inhibitor containing HCV regimens due to the intrinsic qualities of the NS5A inhibitor, drug pharmacology, or effects of the other compounds within the treatment regimen. To enable comparisons of resistance analyses between clinical trials, standardization of RAV definitions and sensitivity cut offs is needed. Further study is needed to understand the role of RAVs present at frequencies below 15% and whether substitutions without an in vitro susceptibility change to the NS5A inhibitor may dilute a clinical signal by RAVs that do confer reduced susceptibility to the NS5A inhibitor.