Received Date : 29-Jun-2016

Accepted Date : 07-Jul-2016

Article type : Commentary

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Editorial: Vidal LL, et al. NS3 protease polymorphisms and genetic barrier to drug resistance of distinct HCV genotypes from worldwide treatment-naive subjects. JVH, 2016, X(X): X-X

A.J. Thompson

Department of Gastroenterology, St. Vincent's Hospital and The University of Melbourne, Australia

Word Count - 674

"The truth is out there" (Fox Mulder, X-files)

HCV has an error-prone NS5B polymerase that generates millions of variant viruses each day. Host selection pressure leads to the emergence of one dominant virus, but many variant viruses co-exist at low frequency as quasi-species, including variants that carry drug resistance associated sequence(s) (RAS). In the setting of monotherapy with a direct acting antiviral (DAA), resistant virus is rapidly selected out leading to virological failure.

Treatment for HCV involves combinations of potent DAAs that target different steps in the viral lifecycle, including the non-structural (NS) proteins 3 (NS3), NS5A and/or NS5B (the RNA-dependent

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jvh.12570

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RNA polymerase). Treatment with sofosbuvir + ledipasvir ±ribavirin (RBV) (SOF/LED) or paritaprevir + ombitasvir + dasabuvir ± RBV (PrOD) is very effective for Gt 1 HCV, with SVR12 results ≥ 95%.In this context, routine screening of treatment-naïve individuals for HCV RAS has not been recommendedfor these regimens (1-3). In contrast, testing for the NS3 Q80K variant is recommended prior to treatment of Gt 1a HCV with simeprevir-containing regimens (1, 2, 4, 5), including simeprevir + sofosbuvir. HCV resistance testing for high level NS5A variants has also been recommended prior to treatment of Gt 1a HCV with grazoprevir + elbasvir by the FDA(1). Such recommendations are driven by the association between these RAS and lower SVR12 rates, but also knowledge of the local prevalence of RAS in the HCV population.

In this issue of JVH, Vidal and colleagues evaluate the prevalence of NS3 RAS in more than 15,000 HCV sequences from treatment-naïve individuals stored in the Los Alamos HCV sequence database [XXX]. Data are clearly presented by RAS frequency using two different thresholds - > 15% (population sequencing) and > 1% (deep sequencing), as well as fold-change in EC_{50} for each RAS-drug pair (± 10-fold). Signature RAS were observed to differ according to HCV genotype and subtype. The frequency of RAS were also observed to vary in different geographic regions.Q80 variants were present in 46% of North American Gt 1a sequences, but < 10% of Gt 1a sequence from Europe, South America and Oceania. NS3 RAS testing for Gt 1a patients is therefore most important for people living in North America who will be treated with simeprevir.NS3 RAS testing can also be recommended for people in regions where treatment continues to involve triple therapy with a PI plus peginterferon and ribavirin.

Knowledge of NS3 RAS prevalence is clinically relevant. At the population level such data may be used to influence recommendations about regimen selection, as well as to guide recommendations about the need for resistance testing in individuals prior to treatment. For an individual, resistance testing is useful if it will change management. As noted, where simeprevir+sofosbuviris first-line for Gt 1a HCV, identification of Q80 variants identifies the need for longer treatment duration ± RBV combination. In low resource settings where simpervir+PR might remain first-line treatment, the identification of Q80 variant might be a reason for treatment deferral pending more effective therapy. In contrast, NS3 RAS testing is not relevant to people with Gt 1 HCV who will be treated with all oral combinations of SOF/LED or PrOD(6, 7).

Similar studies should be performed focussing on the NS5A region. NS5A RAS are now recognized to reduce the overall efficacy of grazoprevir + elbasvir in Gt 1a HCV (8, 9), as well as the efficacy of sofosbuvir + ledipasvir in people with hard to cure characteristics (e.g. treatment-experienced, cirrhosis) or who are planned for short treatment duration (8 weeks) (6).

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In conclusion, the treatment of HCV should involve combination DAA therapy (1-3). HCV resistance testing cannot currently be recommended as a routine clinical test in treatment-naïve individuals given the very high efficacy of first-line regimens (1-3). However, there is merit in using molecular virology to determine epidemiological patterns of HCV RAS frequency and inform local policy regarding resistance testing. HCV resistance testing is indicated at baseline for regimens with a lower genetic barrier to resistance that are being used to treat Gt 1a HCV, particularly in regions where drug-specific RAS are known to be prevalent.

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