Cross-sectional assessment of >20,000 clinical samples submitted for HCV NS3/4A protease inhibitor drug resistance testing in the US

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I. Introduction

Attributes of the first 1500 patient samples tested in a commercially available genotypic NS3/4A protease inhibitor (PI) resistance assay for HCV genotype 1 (GT1) were previously reported. In this analysis, more than 20,000 samples were evaluated to determine if shifts in the prevalence of resistance–associated variants (RAVs) have occurred in samples received for HCV resistance testing after the FDA approval of the first protease inhibitor (PI) direct-acting antivirals in 2011.

II. Methods

HCV GT1a or GT1b clinical samples with viral load submission requirement of ≥ 20,000 IU/mL were sent to Monogram Biosciences for PI resistance analysis. Briefly, the entire NS3/4A region of HCV was amplified by RT-PCR using GT1a or GT1b specific primers (Fig. 1). Samples were analyzed by Sanger sequencing through February 2015, and with the Illumina MiSeq sequencing platform, using a 10% variant threshold, from March 2015 onwards. Amino acid variants relative to either the H77 (GT1a) or Con 1 (GT1b) reference sequences were reported. RAVs were identified and a prediction of drug susceptibility was derived using a rules-based algorithm. The HCV genotype of the NS3/4A region was also determined.

III. Results

- Of the more than 20,000 samples evaluated, 84% were GT1a and 16% were GT1b.
- GT1a sample submissions peaked in 2014 (86%). (Fig. 2)
- The Q80K variant was stable throughout the evaluation period with an average prevalence of 42% and 0.8% among GT1a and GT1b viruses, respectively.
- V36M (3.3%), T54S (2.5%), V55A (2.7%), and R155K (4.1%) were the most commonly identified RAVs, excluding Q80K, among all GT1a samples over the 5 year period.
- V36M and R155K RAVs in GT1a viruses peaked in 2012 (20.2% and 22%, respectively) and then declined by 2016 (1.1% and 2.5%, respectively). (Fig 4)
- Variant combinations V36M + R155K, TS45(2.5%), V55A(2.7%), and R155K(4.1%) were the most commonly identified RAVs, excluding Q80K, among all GT1a samples over the 5 year period.
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- Marked differences in RA V prevalence were not seen among GT1b viruses.

IV. Conclusion

- Trends among PI-specific RAVs observed over a 5 year period reflect utilization of direct-acting agents for hepatitis C.
- Peak PI RAV prevalence was consistent with the prescribing practices of boceprevir and telaprevir and may reflect the emergence of RAVs in samples submitted for resistance analysis following treatment failure or the persistence of RAVs in samples submitted prior to selecting a subsequent treatment regimen.
- Baseline Q80K polymorphism screening for simeprevir use in individuals with GT1a viruses likely accounts for an initial increase in GT1a sample submissions in 2013, peaking in 2014.

V. References

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