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Cross-sectional Assessment of Telaprevir and Boceprevir Resistance-associated Mutations of 500 Clinical Samples Submitted for HCV NS3/4A Protease Inhibitor Drug Resistance Testing in the US

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BACKGROUND

Data on hepatitis C virus (HCV) resistance to the NS3/4A protease inhibitors telaprevir (TVR) and boceprevir (BOC) have been limited mostly to observations from clinical trials and *in vitro* studies[1,2]. Soon after FDA approval of these compounds, a genotypic resistance assay that analyzes the NS3/4A region of HCV became commercially available. Here we report the resistance characteristics of the first 500 patient samples received.

METHODS

HCV genotype 1a (GT1a) or 1b (GT1b) patient samples with viral loads of ≥ 2,000 IU/mL were sent to Monogram Biosciences (South San Francisco, CA, USA) for protease inhibitor resistance analysis using the HCV GenoSure NS3/4A resistance assay[3] (Figures 1,2).

Briefly, the entire non-structural protein 3 (NS3) and 4A (NS4A) region of HCV was amplified by RT-PCR using GT1a or GT1b specific primers, analyzed by population sequencing and compared to either the H77 (GT1a) or Con 1 (GT1b) reference sequences. Resistance-associated mutations (RAMs) were identified and a prediction of drug susceptibility (sensitive, resistant or resistance possible) was derived using a rules-based algorithm. The HCV genotype of the NS3/4A region was also determined. For this analysis, we evaluated the results of the first 500 reported samples.

Figure 1: HCV NS3/4A Sequencing Assay Workflow

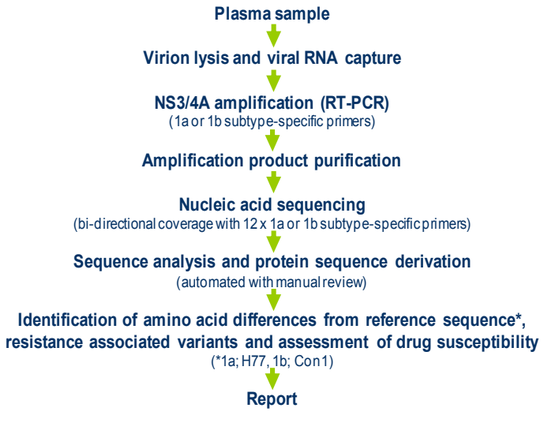


Figure 2: Examples of HCV NS3/4A Sequencing Assay Reports

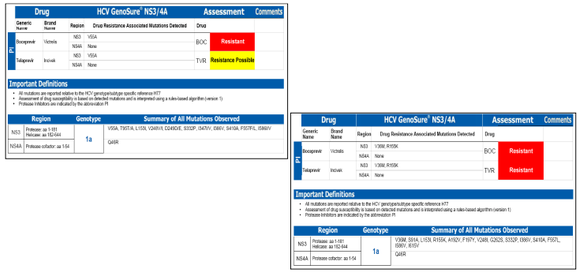


Figure 3: Distribution of Genotype 1a and 1b Subtypes from all Samples

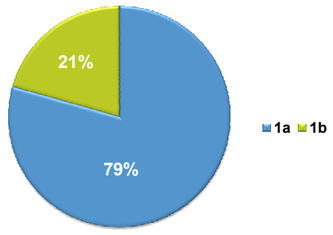


Figure 4: Genotypic Susceptibility Assessments for Telaprevir and Boceprevir

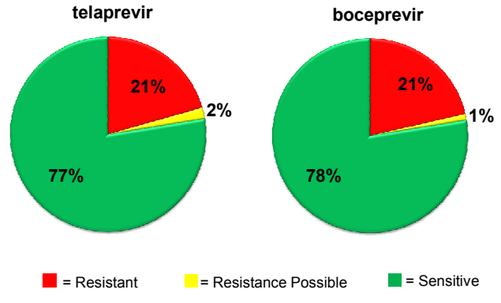


Figure 5: Genotypic Susceptibility Assessments for Telaprevir and Boceprevir based upon Genotype (1a or 1b)

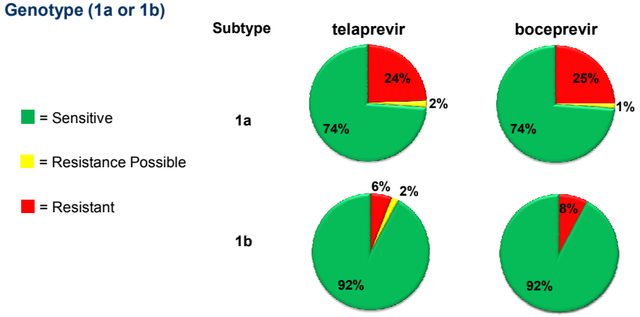


Figure 6: Cumulative NS3 RAM Mutations from all Samples

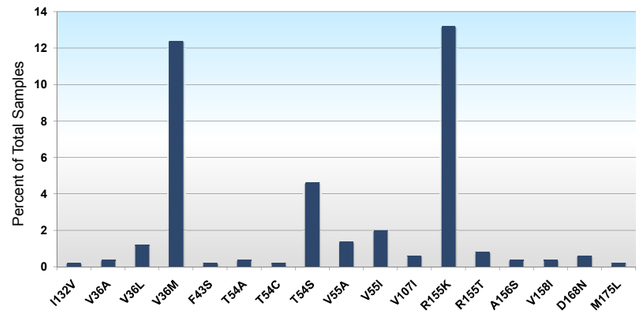
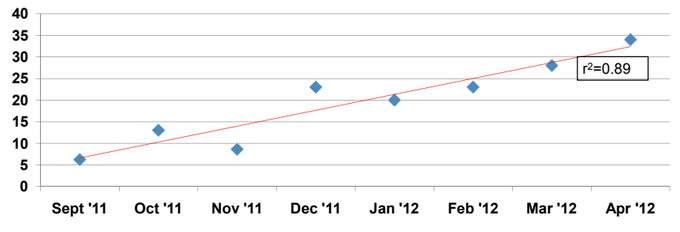


Figure 7: Percent of Patient Samples Demonstrating Resistance Over Time



RESULTS

- Of the 500 samples analyzed, 79% were GT1a and 21% were GT1b (Figure 3).
- Overall predicted resistance to both telaprevir and boceprevir was 21%(Figure 4).
- Predicted resistance to TVR and BOC was 24% and 25% (Figure 5), respectively, in GT1a patient samples, but only 6% and 8%, respectively, in GT1b samples.
- The most commonly observed RAMs for both drugs were R155K (13.2%), V36M (12.4%), and T54S (4.6%) (Figure 6). These mutations were often present in combinations, with R155K+V36M (7.8%) and T54S+V55I (1.6%) occurring most often. The combination of V36M+T54S was observed only in concert with R155K (V36M+T54S+R155K triple mutant) in 1.0% of samples.
- The percentage of patient samples demonstrating resistance to both compounds showed an upward trend of approximately 3.5% per month, increasing from 6.2% in September 2011 to 34% in April 2012 (Figure 7).

SUMMARY & CONCLUSIONS

- The identified TVR and BOC RAMs are in accord with those observed during clinical trials[1,2].
- Our findings demonstrate a significantly higher prevalence of HCV protease inhibitor RAMs among GT1a samples relative to GT1b samples, which is consistent with a higher genetic barrier to TVR and BOC resistance among GT1b viruses.
- The increase in frequency of TVR and BOC RAMs observed over time may reflect the emergence of mutations in patients experiencing treatment failure. This frequency is higher than that observed at baseline during clinical trials and may signify an increasing utilization of resistance testing by clinicians for patients who fail to achieve a sustained virologic response.
- Future updates to this database will determine whether current resistance trends in these initial 500 samples persist over time.

References:

1. Prescribing Information for Incivek™ (telaprevir), Vertex Pharmaceuticals Inc, Cambridge, MA 02139, May 2011
2. Prescribing Information Victrellis™ (boceprevir), Merck & Co., Inc, Whitehouse Station, NJ 08889, May, 2011
3. Anton ED, et al. Validation of an HCV NS3/4A Sequencing Assay for Evaluating Resistance to Boceprevir, Telaprevir and Protease Inhibitor Candidates in a Clinical Reference Laboratory Setting . 62nd AASLD. November 4-8, San Francisco, California. Abstract LB-23.

ACKNOWLEDGEMENTS
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