HCV Drug Development Across Different HCV Genotypes

Patrick Harrington, Ph.D.
Clinical Virology Reviewer
Division of Antiviral Products
U.S. Food and Drug Administration

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Drug Development Challenges for Less Common (in U.S.) HCV Genotypes

- All HCV-infected patients desire safe and effective therapies regardless of their HCV genotype/subtype
- Safety differences across HCV genotypes/subtypes are not expected, but clinical efficacy cannot be extrapolated across genotypes/subtypes
- Not practical to conduct fully powered efficacy trials for HCV genotypes/subtypes that are rare or restricted to geographic locations where clinical trials are not feasible
- Drug resistance remains a concern due to relatively limited pipeline of drugs for less common genotypes

Utility of Phenotype Assays

Characterize antiviral activity

- Demonstrate potential antiviral effect of drug in infected patients
- Compare anti-HCV potency across different genotypes/subtypes

Predict adequate activity at all sites of HCV infection?

- Cannot directly measure intracellular concentrations of active moiety throughout liver

Predict activity against complex HCV populations?

- Clonal assays do not model complex HCV populations in patients
- Population assays reflect predominant or most fit variants in assay

Predict anti-HCV durability?

- Measure shifts in susceptibility for known resistance pathways
- Clinical cutoff for resistance confounded by host, virus and regimen
- Replicon population clearance assays may be informative, but not feasible for routine analysis of patient-derived isolates

Predict efficacy (SVR)?

- Negative predictive value, but poor positive predictive value
  - Multiple examples where SVR rates differ significantly for different HCV genotypes or subtypes despite similar phenotype assay results

Indication for less common genotypes ultimately based on totality of data

- Some direct evidence of efficacy (SVR) generally required for HCV genotype indication, even for rare HCV genotypes
  - Relatively small numbers of subjects, ideally representing most common subtypes in U.S. population within a given genotype
  - Little evidence of virologic breakthrough
  - Conservative treatment duration to limit relapse
- Other supportive information
  - Phenotypic analysis of clinical isolates from multiple subtypes within genotype
  - Selection and characterization of resistance patterns in cell culture
  - Genotypic analysis for the presence of known resistance-associated polymorphisms
  - Short course monotherapy data
  - Evidence of efficacy across diverse genotypes/subtypes
  - Evidence of efficacy in traditionally difficult-to-treat HCV genotypes/subtypes and patient populations
- Labeling
  - Label should describe type and amount of data supporting indication
  - If insufficient data are available to support an indication, information about potential activity could possibly be described in label (Section 12.4)
- Post-marketing studies?