Forum for Collaborative HIV Research

HCV DRAG
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Summary

Utility of Deep Sequencing

- Research use
  - Much quicker than clonal sequencing
  - Applicable for assessing persistence
- Clinical use: unknown
  - No validation of level of resistance that impacts response
    - Naïve patients
    - Retreated patients
  - Value vs. other methods undefined
  - For HCV, results may be very complicated
  - May be irrelevant in context of high cure rates

Deep Sequencing Methodological Issues

- High sampling/PCR bias at low viral loads
  - Deep sequencing not recommended at plasma HCV RNA < 10,000 I.U./mL (maybe even 10^6 I.U./mL)
- Analysis/presentation of results is complicated
- Linkage difficult to determine because of recombination
- Influence of primer on mutation prevalence can be high

Phenotypic Assay Issues

- Clinical utility of phenotypic assays has not been established
  - Size of studies may be prohibitive
- Easy to generate data; hard to prove clinical relevance
  - Easy to miss effects of minor variants
  - Prediction of fitness very difficult
  - Backbone can influence EC_{50}
  - Positive change in EC_{50} meaningful, no change in EC_{50} may not be
  - May give information on effect of polymorphisms

Resistance Mutation Table

- Support for working group moving this effort forward
  - Need data from different groups
- Issue: non-standardized assays
  - If inconsistent results, test is standardized assay?
- Coordinate efforts with other organizations who have the same goal

Clinical Trial Definitions

- Report both LLOQ and LLOD
  - Consistent with assay manuals?
  - LLOD is a moving target
    - Arbitrarily use standardized threshold (eg, 25 I.U./mL) and definition of sample time period
    - Reporting both is step toward harmonization?
    - When possible, utilize retrospective studies to define most appropriate threshold
    - More liberal study design to interrogate effect of LLOQ vs LLOD at early timepoint
    - Followup meeting with diagnostic companies to enforce standard
- Standardized response nomenclature (eg, W4Ud, W8D)
- Standardized pretreatment nomenclature
  - Specify drugs to which patient is experienced

DAA Combination Trials

- POC with IFN-sparing regimens achieved
  - Forms the basis for more aggressive/accelerated approaches
    - Prerequisites for combo DAA studies remain the same
  - Understanding correlates of success (subtype, resistance, etc) important
  - Impetus for going to more difficult to treat and IFN-contraindicated populations
    - Lower SVR rates acceptable
    - Flexibility in study design
    - Complicated PK & PD, DDI
    - Risk of producing or exacerbating decompensation with viral rebound?
    - Encourage early access studies to investigational agents?

DAA Combination Trials

- Other observations
  - Stopping rules may need to be revisited (eg, with quad therapy)
  - Might be useful to understand safety of at least one of the DAAs separate from the 2nd/3rd
  - Role of peg/RBV comparator arm?
    - Incorporate rollover
  - Compare different DAA combos with peg/RBV rescue

HIV/HCV Co-Infection

- Need to define DDIs with ARVs and methadone earlier (same time as statins etc)
  - Need hepatic impairment studies
  - Study transporter interactions in vitro and move quickly into patients
- Start co-infection studies after Phase 2b doses defined
  - Simultaneous with other HCV treatment-experienced studies
  - Include in Phase 3 studies
  - Control group may not be necessary
  - CD4 threshold for early studies: 300

Decompensated & Transplant Patients

- Once DAAs are approved, they will be widely tried in transplant patients in an uncontrolled manner
- Move toward oral DAA combination studies
  - May be easier with renally cleared drugs, eg nucleotides, to avoid DDIs with immunosuppressants
  - Appealing from a viral kinetics perspective

General

- Create glossary of terms for broader community
- Change name of HCV DrAG?

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HCV DRug Development Advisory Board (HCV DRAB)