HCV DRAG

Notes

HCV DRAG Meeting #5
November 2, 2010

HCV DRAG: Liver Biopsies

- Endpoint are virological
  - Biopsies not critical for approval of DAAs
- Role of biopsies
  - Rule out cirrhosis
  - Analyze results with respect to fibrotic stage
  - Biopsies more important in later stages development (Ph 2b/3)
- Difference between EU and US availability and use for non-invasive tests
  - Need to work on increasing access in US, investigate whether tests are under FDA review
  - Invite FDA colleagues from devices to Dec meeting

HCV DRAG: Viral Load Thresholds

- Issues:
  - Official limit of quantitation, no official limit of detection
  - Roche LOQ: 25, Abbott LOQ:12
- Suggestion:
  - Collect both LOQ and detectable/undetectable data
  - Report as either LLOQ detectable or LLOQ undetectable (rather than LLOD)
  - Always use log values (difference of log, not log of difference)
- Need to keep RGT as simple as possible
  - But RGT rules may need to be different for different drug combinations
- Two topics for continued discussion
  - Assay sensitivity
  - Prediction of clinical outcomes (relevant endpoint for stopping rules and response-guided therapy)
    - Risk of using less stringent criteria for RGT – more relapsers
    - Risk of using more stringent criteria for stopping rules – lose benefit of treatment

HCV DRAG: Clinical Trial Definitions

- Terms confused
  - Treatment experienced (IFN, DAA, relapsers etc)
  - Response (RVR, eRVR, EVR etc)
  - Fibrosis stages/cirrhosis
  - High/low BVL
  - Race
  - Drug class (PI, NNI, etc)
- Don’t want the terms to define the development programs
- Need a subgroup to work on consensus definitions?
  - Confer with Adrian Debuschle, Heiner, Don

HCV DRAG: Special Populations

- Begin to study special populations during Phase 3
- Decompensated cirrhosis
  - Dose reduction of pegIFN/RBV an issue
- HIV-coinfected
  - Drug-drug interactions
- Transplants
  - Timing challenge for pretreatment prior to transplant
  - Possible pilot studies in living donor transplants
  - Patient allocation programs? Difficult in US
  - Drug-drug interactions: may need real time drug level monitoring, including for DAAs
- Bleeding disorders
  - Guidance wording: “recommended” pathway in combo with SOC
- Opiate substitution therapy
  - Drug-drug interactions

HCV DRAG: DAA Combo Studies

- Preference to begin in least vulnerable populations (eg, CCs)
  - In more vulnerable populations, use extensive monitoring/adding on SOC
  - EMA:
    - Also open to advanced populations with contraindication to SOC
    - Not recommend nonresponders without immediate need based on fibrosis
- With potent combinations, rebounds more likely after ~4-6 weeks or more, so longer duration than 2 weeks needed to interrogate rebound potential
- Preference for experience with at least one compound with SOC for 12 weeks
- Consider using RBV
- Preclinical
  - FDA: recommend 3 months of single tox work at high doses
  - EMA: likely moving closer to FDA recommendation
- Premature to make decisions on basis of drug classes/genetic barrier, although concern about combo of two relatively weak drugs
- Requirements for triple combos similar to those for double
- Pathways for approval of “weaker” drugs
  - Study in SOC-contraindicated populations
  - Add on to triple
  - Non-inferiority
    - Even could be inferior but still better than placebo, particularly if safety advantage or different resistance profile

HCV DRAG: DAA Dose Reduction

- Not a good option with either TPV or BCV
- Potential examples for dose reductions:
  - If high on Emax curve, eg TMC435 (75 and 150 mg very close)
  - Nucleosides
  - If TDM suggests too high level
  - If VL is undetectable
- Nonlinear PK should be taken into account

HCV DRAG: Stopping Rules

- In general, more aggressive stopping rules will help to prevent increasing fitness of mutants during ongoing replication
- Clinical trial stopping rules can be instructive for clinical practice

HCV DRAG: Intercompany Collaborations

- ACTG mandate from NIAID to expand to other areas of infectious diseases
  - Commitment to funding in mono-HCV infected pts
- Questions about how labeling might evolve out of ACTG studies
  - INDs held by NIAID, analyses by ACTG