Clinical Virology Lessons Learned with Respect to Resistance in Clinical Trials

HCV

DRUG

RESISTANCE

ADVISORY

GROUP

Panel Discussion

Jules O'Rear
Gaston Picchio
Julian Symons
Robert Ralston
Ann Kwong

March 24, 2009
Washington, DC

HCV DRAG: "Lessons learned" agenda

- **What have we learned**
  - Each panelist will take ≤ 5 min to share "lessons learned" from their own experience and observations of other trials (~20 min)
- **Additional questions for the whole panel**
  - Additional questions from the audience (or other panelists) for the whole panel to address; ~10 min/question (~ 20 min)
- **Questions for individual panelists**
  - Specific questions for a panelist; ~5 min/question (~ 20 min)
- **Information from this panel discussion will be included the Clinical Virology Trial Design white paper**
  - Please identify yourself clearly when asking a question so we know who to ask for clarification of comments or questions if necessary

HCV DRAG: Jules O'Rear

HCV DRAG: Gaston Picchio

HCV DRAG: Julian Symons

- Experience with 2 nucleoside inhibitors
  - R1626, prodrug of R1479 (4'-azido-cytidine)
  - R7128, prodrug of PSI-6130 (β-D-2'-deoxy-2'fluoro-2'-C-methylcytidine
- In vitro resistance mutations generated after long term culture selection
  - R1626, NS5B S96T and S96T/N142T
  - R7128, S282T
- Both mutations confer low level resistance and low replication capacity
- R1626 – 6 and 7 patients exhibited viral RNA rebound or non-response in phase 1b study and phase 2a study respectively
  - No evidence of phenotypic resistance, no evidence of S96T or other common amino acid changes by both population and clonal seq. analysis
- R7128 – Similar findings to R1626 in clinical studies
  - NS5B quasispecies data from 42 patients, 3400 NS5B sequences untreated, 800 sequences on-treatment – no evidence of S282T variants

HCV DRAG: Robert Ralston

- Targeted HCV antivirals can select resistant variants quickly
  - 'Resistant' polymorphisms can be detected at baseline in some pts
  - Relation of polymorphisms to response should be evaluated
- Peg-IFN + RBV are critical when used with single targeted agent
  - Ability pt to respond to IFN is likely an important factor for outcome
  - Regimen may impact outcome; need to explore various strategies
- Resistance analysis currently cannot be used to guide therapy in real time
  - Viral load remains key response measure
- Withdrawal of targeted antiviral results in decrease in frequency of some resistance mutations
  - Need to evaluate relationship to in vitro/in vivo fitness
- Resistance monitoring is evolving rapidly
  - Recommendations will need to change with time

HCV DRAG: Ann Kwong

- **Selection of variants**
  - Resistant variants preexist in patients
  - Variants with decreased sensitivity to TVR were selected faster than expected
  - Initial drop in VL is mostly WT virus and lower-level resistant variants
  - Breakthrough is with highly resistant variants (V35M+R155K) and occurs early in naïve patients (most with very low Peg-IFN levels)
  - Genetic barrier at the nucleotide level is important- different in subtypes
  - Unfit resistant variants disappear fast after drug is stopped (A156T>> WT), less fit variants take time (need to monitor)
  - Stopping rules need to be used to prevent furthur evolution
- **TF studies**
  - "Treatment failure" is actually 3 biologically distinct subgroups (true null, partial and relapsers) with significantly different responses to T/PR
  - Need to do the experiment: treatment of TF patients was assumed to have a poor outcome by some,in fact outcome was better than expected
- **IFN and RBV**
  - RBV has a huge impact on breakthrough and relapse
  - Need Peg-IFN plus RBV to eliminate higher level resistance variants
  - No smoking gun observed in sequencing of NS5A and NS5B

HCV DRAG: "Lessons Learned"

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HCV DRAG: "Lessons learned"

- **Questions for individual panelists**
  - Specific questions for a panelist; ~5 min/question (~ 20 min)

HCV DRAG: Ann Kwong

- Resistance selected much faster than expected with highly fit variants
- Initial drop in VL is mostly WT virus and variants susceptible to the level of drug exposure
- Breakthrough is with highly resistant variants (V35M+R155K) and occurs early in naïve patients
- Stopping rules need to be used to prevent further evolution
- "Treatment failure" is actually 3 biologically distinct subgroups (true null responders, partial responders and relapsers) with significantly different outcomes in response to T/PR
- Data trumped loud opinions: treatment of TF patients was assumed to have a poor outcome, relapsers no different than naïve in rate of response
- Need Peg-IFN plus RBV to eliminate higher level resistance variants
- RBV has a huge impact on breakthrough and relapse (big surprise)
- Genetic barrier at the nucleotide level is important and can affect response with different subtypes
- Unfit resistant variants selected under drug pressure disappear fast after drug is stopped (A156T>> WT quickly)

HCV DRAG: "Lessons Learned"

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