Forum for
Collaborative HIV Research

Summary

Dale Kempf

Next Steps

- New leader for phenotype working group
- Reorganization of clinical working group
- Create ResistLit DB WG (*Resistance Literature Database working group)*
- Create HCV resistance CME working group
- Next steps on collaborative HCV resistance database
- Publication of meeting outcomes (manuscript #3)
- Next meeting (Autumn 2009)
  - Focused topic

Clinical Working Group

- Clinical working group members
- Clinical working group head
- Subgroups?
  - HIV co-infected
  - Others?

Process

- Categorize issue and questions into one of following:
  1. Immediate recommendation needed to guide process in right direction
  2. Recommendation based on discussions within working groups and between WG's and DRAG
  3. Multiple possibilities to be described by working group with pro/con and context
  4. Insufficient data/methodology at this time, noted as issue

Some issues

- Predictability of RVR for SVR with SM therapy
- Defining fitness: *in vivo* vs *in vitro*
- How do we understand barrier to resistance?
  - Genetic vs fitness vs pharmacologic
  - Selection vs evolution?
- Studies in treatment-experienced patients
  - Three types of patients
  - Is risk of resistance higher than in treatment-naïve populations?
  - Is the outcome of resistance more severe than in treatment-naïve patients?

Some more issues

- Length of monotherapy studies
- Variability in susceptibility to small-molecule agents:
  - Across genotypes
  - Within a subtype?
  - (Is this an issue for the PWG to address?)
- Differences in resistance patterns between GT-1 subtypes
- Nomenclature: polymorphisms vs mutations
  - (Is this an issue for the SAWG to address?)

Yet some more issues

- Lead-in trial design
  - For treatment-naïve patients?
  - For treatment-experienced patients?
  - Are we ready for “personalized medicine”?
  - What is the impact on power calculations
- Re-treatment after small molecule drug failure
  - Informed consent: does exposure to one drug disqualify that patient for a future protocol?

And even some more…

- To what extent can results with IFN/RBV be extrapolated to IFN-free small molecule drug combos?
  - What is the contribution of SOC?
- We want to reduce risk with respect to future treatment options
  - But, what is that risk? Is rebound truly detrimental?
- Treatment-experienced populations
  - Is a combination of a small molecule with SOC truly "functional monotherapy"?

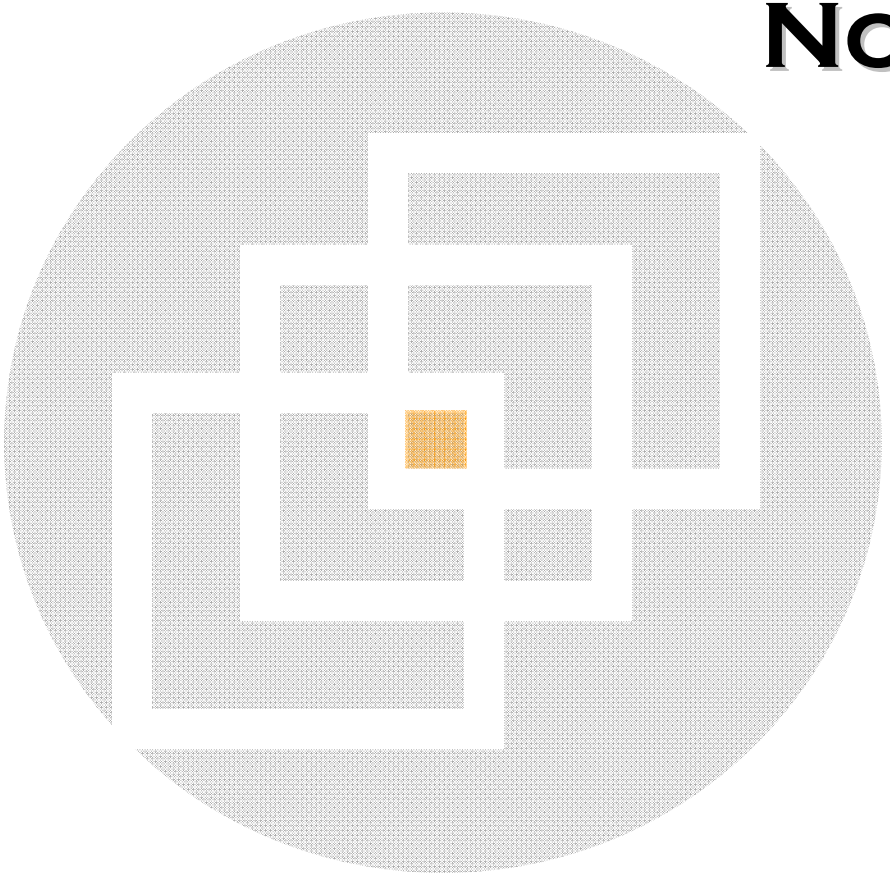
And a few more

- Studies in pts with decompensated cirrhosis/transplant candidates and other high-need populations (*eg*, HIV coinfected)
- 24-week standard for defining SVR: should it be modified to 12 weeks?
- Viral persistence:
  - Which data are needed? For how long?
  - Stopping rules for clinical trials
  - Most appropriate assay (topic for SAWG?)

And finally…

- Communication of resistance information to physicians
  - Need standarization of the way that resistance prevalence is reported

Notes



Forum for
Collaborative HIV Research

Clinical Virology Lessons Learned

Resistance in Clinical Trials

Combinations with SOC

Lead-in Trial Design

Lessons Learned: Jules O'Rear

- Replicon and enzyme systems good for characterizing resistance and identifying pathways
- Question: predictability of RVR for SVR
  - PROVE 2 suggests perhaps not for small molecule drugs
  - Some drugs show rapid rebound
- Don't confuse potency with durability
  - Potency: effect on WT virus
  - Durability: related to effect on mutants
- PROVE 3 study showing higher rate in experienced patients
- Lead-in trial design
  - Steady state of IFN and/or RBV
  - Important to have comparator

Lessons Learned: Gaston Picchio

- Statistical methods of identifying mutations associated with resistance
  - Poisson vs binomial distribution
- Non-genotype 1 HCV – challenge to amplify sequences from GT 2, 3, 4

Lessons Learned: Julian Symons

- Generating resistance to nucleosides in vitro is difficult
  - Have to distinguish between cell toxicity and lack of resistance
- Finding evidence of resistance in vivo with nucleosides has been difficult

Lessons Learned: Rob Ralston

- Difference between replicon and clinic:
  - Observe more mutations in vivo
  - More likely to get double mutants clinically
- Polymorphisms with reduced susceptibility can be detected at baseline
  - Relationship to response needs to be evaluated
- Ability to respond to IFN is critical
  - Lead in treatment?
- Resistance testing can't guide in real time
- Frequency of some mutants decline after therapy is stopped
  - Need to evaluate in vitro/in vivo fitness

Lessons Learned: Ann Kwong

- Resistance is selected much faster than expected with highly fit variants
  - Need to look much earlier than 14 days
- 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
- Genetic barrier is different by GT1 subtypes
- Unfit resistant variants selected under drug pressure disappear fast after drug is stopped (A156T>> WT quickly)
  - Sometimes see correlation of in vivo fitness to in vitro RC
- Stopping rules need to be used to prevent further evolution

Lessons Learned: Ann Kwong

- Treatment failure (TF) studies
  - "Treatment failure" is actually 3 biologically distinct subgroups (true null responders, partial responders and relapsers) with significantly different outcomes in response to T/PR
    - Lead in design can help to define these populations
  - Data trumped loud opinions: treatment of TF patients was assumed to have a poor outcome, relapsers no different than naïve in rate of response

Lessons Learned: Ann Kwong

- 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

Lessons Learned: Discussion

- How does one define a high or low genetic barrier?
  - Will probably ultimately be determined clinically rather than in vitro
  - Important to distinguish “genetic barrier” (ie, # of mutations) vs “fitness”
  - Also have “pharmacological” or “exposure” barrier
  - Important to have clear definition of these terms
    - “Selection” vs “evolution”?

Forum for
Collaborative HIV Research

Clinical Trial Design

Regulatory Perspective

Definitions of Treatment Experience

Clinical Trial Design: Jules O'Rear

- Limits to monotherapy
  - Can see rebound in 3 days
- If variable activity across genotypes, then concerned about spectrum of activity within a genotype or subtype

Clinical Trial Design: Jules O'Rear

- Categorize treatment experienced patients
- Combo small molecule drugs on top of SOC, particularly in treatment exp pts
  - Consideration of mathematical models of viral heterogeneity
    - 0.1 to 1 mutation per replication event
- Safety signal could confound development of both drugs
  - Have to be careful when to start combos

Clinical Trial Design: Natalie Morgensztejn

- The risk of resistance should be the leading issue when designing trials
- Stepwise approach:
  - GT1 naïve or relapse, no advanced fibrosis, not coinfected with HIV
- RVR & EVR defined prospectively

Clinical Trial Design: Ira Jacobson

- Need to begin talking about IFN-free combos
  - What is “contribution” to SOC needed for studying SM combos?

Clinical Trial Design: Resistance Concerns/Objectives

- Learn lessons from past drug development including HIV
  - Avoid a paradigm of sequential "monotherapy"
    - Does this mean in combo with SOC?
  - Reduce risks for clinical trial participants with respect to future therapeutic options
    - Has everything been done to reduce risk?
- Remain aware that HCV is NOT HIV and that we need to base decisions from data generated in HCV studies

Clinical Trial Design: Specific Issues

- Duration of monotherapy in initial proof-of-concept studies
  - 3 day rule of thumb, not set in stone
  - If mutants preexist, is there really a difference between 0 and 7 days of monotherapy
- Appropriate sequence of development in patient populations: naïve-relapsers-null responders
  - Study naives first for POC (least vulnerable can more easily be salvaged with IFN/RBV)
  - May be different for second generation compounds
- Impact of selection of drug resistance on use of subsequent regimens: cross-resistance and persistence
  - Will be helpful in label
- Mutational barrier needed for non-interferon based regimens
  - How much data needed first?
  - Could be different for null responders

Definitions of Treatment Experienced Populations

- Naïve: received no prior therapy for HCV
- Null Responder: <2 $\log_{10}$ reduction in HCV RNA at Wk 12 on a PEG-IFN/RBV regimen
- Partial Responder: ≥ 2 $\log_{10}$ reduction in HCV RNA at Week 12, but not achieving HCV RNA undetectable at end of treatment with a PEG-IFN/RBV regimen
- Responder Relapser: HCV RNA undetectable at end of treatment with a PEG-IFN/RBV regimen, but HCV RNA detectable within 24 weeks of treatment follow-up

Clinical Trial Design: Concerns

- Adding one drug to PEG-INF/RBV in previous null responders
- "Functional monotherapy"? Is this a useful term for combinations with PEG-IFN/RBV?
  - RBV has no antiviral activity alone—but increases antiviral effect of IFN
- How much data (SVR and resistance data) is needed before studying treatment-experienced patients?
  - Some week 12 EVR in treatment naïve
  - Some SVR data before going into Phase III
- How much data (SVR and resistance data) is needed before combination therapy?
  - If you can't take IFN/RBV at all, shorter term data may be acceptable
- Prioritize issues for the regulatory agencies

Clinical Trial Design: Discussion

- Are there differences in emergence of resistance between 1a and 1b?
  - For telaprevir, more frequent with GT1a, and patterns are different
  - For boceprevir: R155K more common in GT1a
  - What about in exp patients?
    - If true null responder, preexisting variants may have an effect (if no IFN component)
- Need to be careful about conclusions of SVR with GT1a vs GT1b

Clinical Trial Design: Discussion

- Are there different patterns of early vs late breakthrough?
- Viral load is currently best resistance test
- Nomenclature of polymorphisms vs resistance mutations vs compensatory mutations

Clinical Trial Design: Discussion

- How do we account for the contribution of pegIFN/RBV?
  - Lead-in phase??
  - Should we encourage personalized treatment (RVR treated differently than null responders)
    - Impacts power calculations for study design
    - Maybe not relevant for clinical practice?
    - If we had that information, would we know what to do with it; would each drug be the same?
- Do we have information on re-treatment after small molecule failure/resistance

Clinical Trial Design: Discussion

- Monotherapy period – 3 or more days?
  - What is incremental value of >3 days?
  - Will likely be different for non direct-acting antivirals
- Naïve population also consists of non-responders, so exposing them to risk as well
- IFN-intolerant populations: could be good target population for small molecule combos

Clinical Trial Design: Discussion

- Use of adaptive designs for small molecule combinations: “folding in additional drugs over time”
- Should we be going faster into difficult to treat populations because of higher risk of morbidity in these individuals?
  - Should industry be pushed to go into special populations faster? (early PK interaction studies)
- Need to have data in special populations by time approval for naïve populations, to avoid wide use with no data

Clinical Trial Design: Discussion

- By being cautious, we are gearing studies toward patients in less need of treatment
- Different "ethical standard" in US/EU than in other regions of world
- Under what conditions could drug be developed without SOC combo paradigm?
- Studies in pts with decompensated cirrhosis/transplant candidates
  - Compassionate use programs?
  - Possibility of different safety profile

Clinical Trial Design: Discussion

- Would like to see studies in HIV coinfected pts
  - Different safety profile?
- 24-week SVR standard: should it be modified to 12 weeks? (98% relapse within 12 weeks)
  - SVR12 could be used for going into further studies
  - Followup duration may change for future compounds

Clinical Trial Design: Discussion

- Role of immune clearance in HCV is unknown
  - Will impact number of drugs needed and genetic barrier
- Messages from regulatory needed:
  - Encourage studies in patient populations of higher need
  - Reassurance that those findings will not impact treatment-naïve programs

Forum for
Collaborative HIV Research

Long Term Follow-up of Drug Resistance

Long Term Followup: Discussion

- With long-lived mutations, need data on both viral load and prevalence
  - Length of followup is data-driven
  - Long-term followup is restricted to those with documented resistance
  - What proportion of resistance merits followup?
    - Or what absolute IU merits followup?
  - Can't generalize across class, maybe not even within class

Long Term Followup: Discussion

- What is the clinical significance of persistent mutants?
  - In combo with another SM, could be useful to re-treat with same class
- There is no durable archive of resistance
  - Need to reduce duration of failing therapy
    - Related to hepatocyte turnover?

Long Term Followup: Discussion

- Enrollment of patients who have failed a different drug
  - Usually disqualified
  - Cross resistance concerns
- Monitoring persistence:
  - Better to monitor decay rate in individual subject or to analyze populations at some time point?
  - What is the endpoint? No mutant by population sequence?

Forum for
Collaborative HIV Research

Hepatologists Meet Virologists

Reinfection *vs.* New Infection

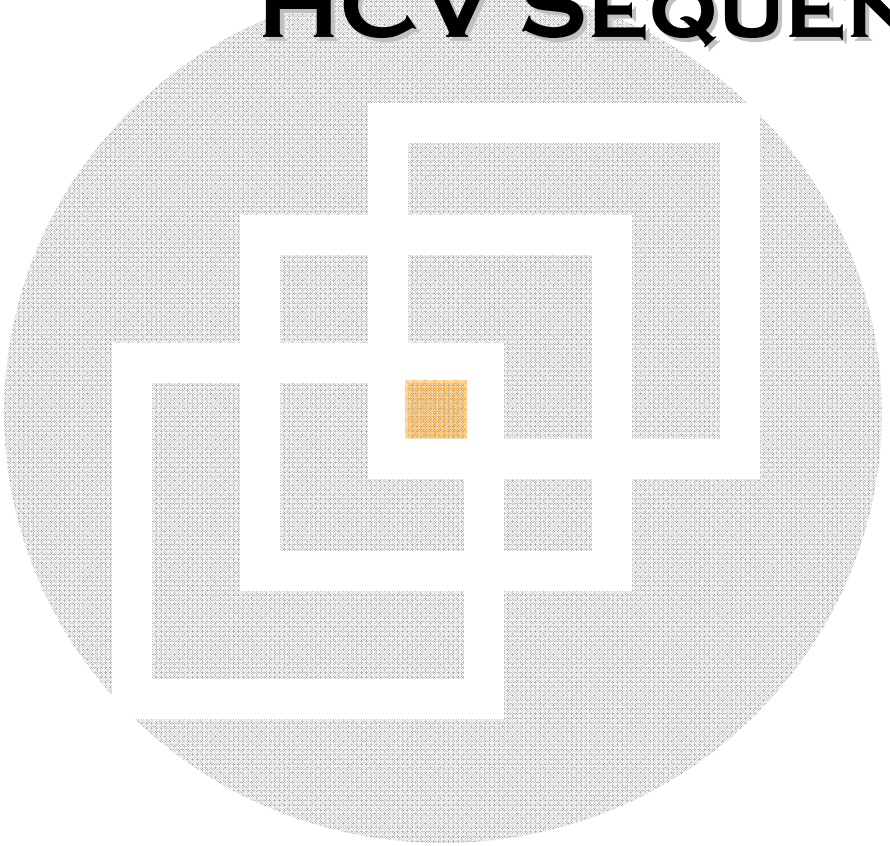
Treatment of Experienced Patients

Hepatologists Meet Virologists: Discussion

- How best train treating physicians about resistance?
  - Guidelines vs education
- Reporting of resistance data to physicians
  - Industry is in a position to take a leadership role
  - Opportunity to make information in label and other sources consistent
  - Won't be applicable until we know how to use the information
  - Need standarization of the way resistance prevalence is reported
  - VL and drug level monitoring may be more useful at present

Forum for
Collaborative HIV Research

HCV Sequence Database



HCV Resistance Sequence DB

- Need for framework allowing collection of HCV drug resistance information in consistent, standardized format
- Meeting in Paris, Feb 2008 w Japanese, European and Los Alamos database representatives
- Mechanisms for integrating a new HCV resistance database into existing structures?

HCV Resistance DB

- Protected section for HCV drug resistance sequences within a public warehouse that all three databases feed into
- A 4th entity: HCV drug resistance info, and all 4 feed into a public warehouse
- Restricted access:
  - Baseline vs follow up sequences

Proposed Next Steps

- Needs assessment and interest on part of pharma
- Other possible funding sources: ANRS, NIH, EU
- Discuss governance structure and access