Forum for Collaborative HIV Research

Hypothetical Case Study: Combination Therapy Trial of Vorinostat and Gene Therapy Modified CD8+Cells

Forum HIV Cure Project: Focus on The Regulatory Pathway

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Co-development of Two or More Unmarketed Investigational Drugs for Use in Combination

(Based on CDER Guidance for Industry, June 2013)

Presented by Jeff Murray

Co-development should ordinarily be reserved for situations that meet all of the following criteria:

- ✓ Combination is intended to treat a serious disease or condition
- ✓ Compelling biological rationale
- ✓ Compelling reason agents cannot be developed individually
- ✓ Data suggesting that the combination may provide a significant therapeutic advance over available therapy and may be superior to the individual agents.
  - A full nonclinical characterization of the activities of the investigational drugs, individually and in combination, OR
  - A short-term clinical study using an established biomarker

Phase 1: Early Human Studies

- The safety and PK profile of each individual new investigational drug should be characterized in phase 1 studies
- If there is a useful measure (e.g., biomarker) of pharmacologic activity, it will be important to determine dose-response for that measure
- If testing in healthy volunteers is not possible, the safety profile of the individual drugs should be evaluated in patients with the disease of interest
- These safety data will guide decisions in later studies about starting doses, dose escalation increments, and final dose selection

Phase 2: Proof of Concept

- Scenario 1: Each drug alone has activity and can be administered individually
  - Standard factorial design (AB vs A vs B vs SOC or placebo)
- Scenario 2: One drug is active alone and one is inactive (e.g., PK enhancers)
  - AB vs A vs SOC or AB+SOC vs A+SOC vs placebo + SOC
- Scenario 3: Components of the combination cannot be administered individually
  - In vitro studies, in vivo animal models, or phase 1 or other early clinical studies indicate that the individual new investigational drugs in the combination cannot be administered separately in clinical trials in the disease of interest
  - POC evidence for the combination ordinarily should come from a study directly comparing the combination (AB) to SOC*.

*In the case of HIV Cure there is no current SOC option

Hypothetical Case Study:

Sharon Lewin, Monash University

Assumptions

- Vorinostat (VOR)
  - Shown to stimulate virus expression in vivo, but no demonstrable effect on the viral reservoir
- Gene therapy modified $CD8^+$ cells (CD8)
  - Chimeric antigen receptor modified $CD8^+$ cells with the antigen binding site from a broadly neutralizing anti-HIV antibody
  - Shown to be safe and persists at a detectable level for 6 months in virally suppressed HIV-infected patients on therapy
  - Displays a trend towards a decrease in cell-associated HIV RNA in transfused HIV-infected patients

Population

- Chronically HIV infected individuals on suppressive conventional ARV therapy with HIV RNA <50 cps/mL for two years

- $CD4^+$ cell count >350

Study Design
Four arm (1:1:1:1) RCT

- Arm 1: CD8 infusion followed by VOR every 3 days for 4 weeks
- Arm 2: Sham infusion followed by VOR every 3 days for 4 weeks
- Arm 3: CD8 infusion followed by VOR placebo every 3 days for 4 weeks
- Arm 4: Sham infusion followed by VOR placebo every 3 days for 4 weeks

Primary and Secondary Outcomes

- Primary Endpoint – Safety

- Secondary Endpoint: Efficacy
  - IUPM, pre-therapy and post 4 weeks of VOR or placebo
  - Cell-associated HIV RNA in $CD4^+$ cells
  - Cell-associated HIV DNA in $CD4^+$ cells

    AND
  - Time to viral rebound

    OR
  - Time to viral set point with a fixed duration 16 week ATI post 4 weeks of VOR or placebo

Panel Discussants

- Moderator: Sharon Lewin (Monash)

- Panelists:
  - Yuman Fong (COH, RAC)
  - Ilan Irony (CBER)
  - David Margolis (UNC)
  - Jeff Murray (CDER)
  - Matt Sharp (CAB)
  - Geoff Symonds (CALimmune)

Panel Discussion I

1. What initial data are needed for VOR or other latency activating agents prior to a combination trial
2. How to establish the timing of the kick and the kill?
3. What is the appropriate outcome other than safety?
   - Is the IUPM assay required? Is there an easier assay?
4. Is the placebo arm (#4) required if the goal of the trial is to test combination vs. individual intervention?

Panel Discussion II

5. Should all of these trials include a treatment interruption?
6. Should this trial involve treated acutely-infected individuals or chronically-infected, or both?
7. What effect size is meaningful?
   - If a very large effect is needed, then a smaller sample size will be sufficient, but risk missing a small signal