

# Utility and Predictors of Rapid Viral Response (RVR) in HCV & HCV/HIV Coinfected Hemophiliacs

Philippe J. Zamor<sup>1</sup>, Norah J. Shire<sup>1</sup>, Susan D. Rouster<sup>1</sup>, M. Elaine Eyster<sup>2</sup>, Kenneth E. Sherman<sup>1</sup>, and Multicenter Cohort HCV Study Group

<sup>1</sup>University of Cincinnati, Cincinnati, OH, USA, <sup>2</sup>Penn State Medical Center, Hershey, PA, USA

## Abstract

**Background:** Rapid viral response (RVR) has been identified as a useful predictor of treatment outcome among patients with hepatitis C virus (HCV) infection. Its utility in HCV monoinfected and HCV/HIV coinfecting hemophilic subjects remains unexplored. We evaluated early predictors of viral response based upon viral kinetic modeling parameters from a prospective treatment trial.

**Methods:** Hemophilic subjects with HCV or HCV/HIV coinfection were enrolled in a prospective trial, treated with pegylated interferon  $\alpha$ -2a qw + ribavirin 800 mg qd for 48 weeks, and followed for 24 weeks. Sustained viral response (SVR) was defined as HCV RNA not detectable by PCR at end of follow-up. RVR was defined as HCV RNA negative after 4 weeks of treatment. Viral kinetic parameters were calculated using data derived from serum samples collected at multiple time points during the first 28 days of treatment.

**Results:** Twenty-three subjects were enrolled in the trial. Twelve were HCV monoinfected and 11 were coinfecting. Most were male and Caucasian (91%). Mean age was 36.9 years. 10.5% had advanced fibrosis (F3-4). Mean HCV viral load was 6.6  $\log_{10}$  IU/mL prior to start of treatment. Genotype 1 or 4 was present in 65% of subjects. Median baseline CD4 was 746.4 cells/mm<sup>3</sup> in monoinfected and 695 cells/mm<sup>3</sup> in coinfecting subjects. SVR was achieved in 8/22 subjects (36.4%) who had detectable virus at the end of pre-treatment screening (1 subject was virus negative prior to first dose). ITT analysis demonstrated SVR in 45.5% versus 27% of those with monoinfection and coinfection, respectively. RVR occurred in 9 subjects and was observed in 7 of 8 SVRs (87.5%) This association was highly significant (p=0.0004). Viral kinetic parameters were estimable for 18 subjects. Best subset regression of calculated variables suggested strong RVR association with  $\epsilon$  (viral efficacy) and  $\lambda_2$  (2<sup>nd</sup> phase decline slope). Mean epsilon was 0.926 (S.E.M.=0.067) among those with RVR and 0.53 (S.E.M.=0.12) among those without.  $\lambda_2$  was also significantly greater among subjects with RVR (p=0.006).

**Conclusion:** RVR was highly predictive of SVR in both HCV monoinfected and coinfecting hemophilic subjects. Kinetic modeling provided evidence for a strong association between RVR and early viral clearance efficacy ( $\epsilon$ ) and with Phase 2 viral decline slope. Larger prospective trials may permit identification of response and non-response parameters within the first week of treatment.

## Background

•HCV/HIV Coinfection is an important cause of morbidity/mortality

•Pivotal trials have established pegylated-interferon (PEG-IFN) + ribavirin as the standard of care for treatment of HCV in the setting of HIV

•Sustained viral response (SVR) rates are lower in coinfecting vs. HCV monoinfected patients<sup>1</sup>

•Rapid viral response (RVR) has been identified as a useful predictor of SVR in HCV monoinfected subjects

•There are limited data regarding the utility of RVR in HCV/HIV coinfecting individuals

## Hypothesis

•RVR will predict SVR in both HCV monoinfected and HCV/HIV coinfecting hemophilic subjects

•Viral kinetic parameters can be used to predict RVR very early following treatment initiation

## Methods

### Study Population and Treatment Intervention

•Hemophilic subjects from four tertiary centers

•All subjects were treated with peg-IFN  $\alpha$ 2a 180 mcg q wk/ribavirin 800 mg qd for 48 weeks and followed for 24 weeks to determine SVR rate

### Key Inclusion Criteria

•HCV or HCV/HIV-1 coinfection

•Documented hemophilia A or B with exposure to blood products before 1987

•Liver biopsy within 6 months of treatment initiation

•Subjects on stable HAART regimen for at least 8 weeks prior to study

### Key Exclusion Criteria

•Hgb <10g/dL

•CD4+ T cells <200 cell/mm<sup>3</sup>

•No other active liver disease: HBV, alcohol use, etc

•Prior treatment with interferon or ribavirin

•Evidence of decompensated liver disease

### Viral Kinetics

•Biphasic model for HCV kinetics was applied to both mono- and coinfecting subjects<sup>2</sup>

•First phase of decay occurs during the first 48 hours of treatment, beginning at time  $t_0$ .  $V_0$  is viral load at  $t_0$ . C is the rate of clearance of free virus per day.  $\lambda_1$  is the slope of first phase decline.  $\epsilon$  is the treatment efficacy at blocking production or release of virions by infected cells (0[no efficacy] - 1[100% efficacy])

•Second phase modeled through 28 days of treatment.  $\delta$  is the infected cell death rate, and  $\lambda_2$  is second phase decline. If  $\lambda_2$  is not >0, patient predicted to be never free of virus

### Response Definitions

•RVR (Rapid Viral Response): HCV RNA negative after 4 weeks of treatment

•SVR: HCV RNA negative 24 weeks after treatment completion

## RESULTS

### Study Population Demographics

	HCV Monoinfected N = 11	HCV/HIV-1 Coinfected N = 11
<b>Gender</b>	Male = 10	Male = 11
<b>Age</b>	Mean = 38 (19-52)	Mean = 35.5 (22-43)
<b>Race</b>	Caucasian = 9 African-American = 1 Other = 1	Caucasian = 10 African-American = 1
<b>Baseline CD4+ (cells/mm<sup>3</sup>)</b>	Mean = 746.4 Median = 661 Range = 421-1,217	Mean = 695 Median = 703 Range = 305-1,274
<b>Baseline HIV-1 VL (copies/mL)</b>	N/A	Mean = 1842 Median = 75 Range = 75-9,843
<b>Baseline HCV VL (log<sub>10</sub> IU/mL)</b>	Mean = 6.74 Median = 6.76 Range = 5.78-7.53	Mean = 6.65 Median = 6.49 Range = 6.07-7.43
<b>HCV Genotype</b>	1/4 = 7; 2/3 = 4	1/4 = 8; 2/3 = 3

### SVR

•Achieved in 8/22 subjects (36.4%)

•ITT analysis of SVR: 45.5% (mono-infection) vs. 27% (coinfection)

### RVR

•Occurred in 9/22 subjects (40.9%). 1 subject with RVR did not achieve SVR

•Was seen in 7/8 (87.5%) subjects with SVR; highly statistically significant (p=0.0004)

### Viral Parameters

•Best subset regression of calculated variables suggested strong RVR association with  $\epsilon$  (viral efficacy) and  $\lambda_2$  (2<sup>nd</sup> phase decline slope)

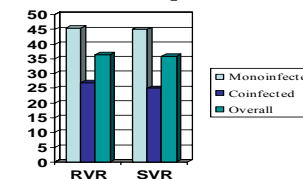
•Mean epsilon ( $\epsilon$ ): RVR 0.926 (S.E.M.=0.067), no RVR 0.53 (S.E.M.=0.12)

• $\lambda_2$  was significantly greater among those subjects with RVR (p=0.006)

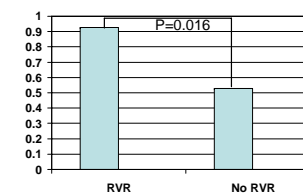
•Achieving RVR was 90% sensitive and 93% specific to predicting SVR

•Viral parameters could not be calculated for all patients (4/22) for various reasons: viral rebound which prohibited model convergence and another estimates unable to bootstrapped

## Treatment Response



## Predictors of RVR: viral efficacy ( $\epsilon$ )



## Other Analyses

•Multiple regression analysis revealed no correlation between pretreatment viral load and RVR or SVR, although the study was not powered for this

•When stratified by genotype, HCV RNA decline at 48 hours was statistically significant for geno 2/3 (p=.02), but not for geno 1/4 (p=.70)

•Viral clearance, infected cell death rate, and phase 1 slope did not demonstrate significant correlation in predicting RVR

## Summary

•RVR was highly predictive of SVR in both HCV monoinfected and coinfecting hemophilic subjects

•Kinetic modeling provided evidence for a strong association between RVR and early viral clearance efficacy ( $\epsilon$ ) and with 2<sup>nd</sup> phase viral decline slope ( $\lambda_2$ )

## Conclusions

•While indicators of RVR have been identified and is a known predictor of SVR, larger studies are needed to validate its use in the coinfecting population and possibly identify critical parameters to guide treatment

•If validated, certain indices can be used to assess treatment efficacy and be used as an indicator whether or not one will respond to treatment and consider stopping therapy in those who treatment is likely to fail

•These viral kinetic parameters can also be further studied to identify possible correlation with other markers such as host genetic factors and viral quasispecies evolution

## References

- Shire NJ, Welge JA, Sherman KE. Response rates to pegylated interferon and ribavirin in HCV/HIV coinfection: a research synthesis. *Journal of Viral Hepatitis* 2007;14:239-248.
- Shire NJ, Horn PS, Susan SD, Stanford S, Eyster ME, Sherman KE, and the Multicenter Hemophilia Cohort HCV Study Group. HCV Kinetics, Quasispecies, and Clearance in Treated HCV-Infected and HCV/HIV-1-Coinfected Patients with Hemophilia. *Hepatology* 2006;44:1146-1157.