Evaluation of Rapid and Sustained Population Viral Response Rates Predicted Under Hepatitis C Virus Dynamic Models

Kyle Baron¹, Patanjali Ravva², Vivek Purohit², Matthew M. Riggs¹, Marc R. Gastonguay¹
¹Metrum Research Group, Tariffville, CT; ²Pfizer Inc., New London, CT

Objectives

The objective of this study was to compare both short and long-term population-level viral response predicted under two HCV dynamic models [3, 13] with observed response rates in a meta data set compiled from published clinical reports.

Methods

• HCV dynamic models published by Dahari et al. [3] and Snoeck et al. [13] were used to simulate individual-level viral load versus time profiles in all HCV genotype-1 infected patients (N=5000).
• Viral load profiles simulated in R using the lme4() function in the lme4 library.
• Simulation Assumptions:
  1. Standard of care regimen: pegIFNα-2a (180 ug per week) + ribavirin (13 mg/day) x 48 weeks
  2. Viral load limit of detection: 100 copies/ml.
  3. ED[DOSE]/ED[DOSE], all between-subject variability parameters same for Snoeck and Dahari models
• Individual-level random effects uncorrelated; no residual unexplained variability in observations.
• SVR predictions were somewhat over-optimistic when dropout was based only on insufficient viral response. This 10% adjustment to responder rate was required after week 48 to match simulated and observed sustained viral response rates.

Results

• 5-10% of simulated subjects had a baseline viral load that was below the lower limit of detection.
• Overall dropout rate due to insufficient viral response was: Snoeck: 33.4% (22.5% at 12 weeks and 11.5% at 24 weeks); Dahari: 36.4% (29.5% at 12 weeks and 12.3% at 24 weeks).
• Among subjects with undetectable simulated viral load at 72 weeks, 28.8, 81.6, and 97.5% also had undetectable viral load at 12, 24, and 48 weeks after starting treatment.
• 5-10% of simulated subjects had a baseline viral load that was below the lower limit of detection and were excluded from the data set.

Conclusion

• Model-predicted viral response rates were similar for both models.
• Simulated dropout rates due to insufficient viral response were higher than observed rates [3, 13].
• SVR predictions were somewhat over-optimistic when dropout was based only on insufficient viral response at 12 and 24 weeks.
• An additional -10% adjustment to responder rate was required after week 48 to match simulated and observed SVR rates.
• Further development of an appropriate time-to-event dropout model is needed to forecast viral response time-course appropriately under standard of care therapy.
• Viral dynamic models need further exploration before they can be used as decision making tools in drug development.

References