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

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Modeling and HCV drug development

• Model-based simulation is playing a key role in:

- Understanding HCV and its treatment
- Efficient development decisions for new therapeutics
- Regulatory decisions
- Important to qualify performance of published models for population simulation

Objective

- Evaluate model-predicted early and late viral response rates
 - Simulate from parametric models
 - Compare with aggregate clinical SOC data
- Snoeck et. al. (2010) "A Comprehensive Hepatitis C Viral Kinetic Model Explaining Cure"
 - Population-based analysis
 - Large clinical data set
- Model adapted from Dahari et. al. (2007) "Modeling hepatitis C virus dynamics: Liver regeneration and critical drug efficacy". (figure 2)
 - Plausible fixed-effect parameter set
 - Random effects structure borrowed from Snoeck et al.

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Methods

Monte Carlo simulation methods

- Model equations implemented in R
 - Lsoda solver in deSolve() package
 - Univariate parameter distributions
- Standard of care intervention
 - peg-IFN-alfa-2a 180 $\mu g/week$ + RBV 13 mg/kg/d x 48 weeks
 - Constant treatment over time
- Dropout criteria
 - 12 weeks: detectable VL & < 2-log drop from baseline
 - 24 weeks: detectable VL
 - Limit of detection: 100 copies/mL
- Response rate versus time
 - 4, 12, 24, 48, 72 weeks
 - Responder: undetectable viral load & not previously dropped
 - Compare with meta data set

SOC meta data set

- 11 trials
- Years: 2002 to 2010
- peg-IFN-alfa-2a + RBV
- Weighted response rate by week
- 95% CI by week from beta-binomial analysis in WinBUGS



Simulated dropout due to insufficient response (%)

Model	12 weeks	24 weeks	Overall
Snoeck et. al.	22.5	11.9	34.4
Modified Dahari et. al.	35.2	1.2	36.4

Simulated viral load versus time (N=250)



Viral response rates versus time



Viral response rates versus time



Viral response rates versus time



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Summary

- Simulated response rates matched aggregate data well up to 48 weeks - under unrealistic assumption that all drop is due to insufficient response only
- Simulated SVR rates were biased unless a simplistic dropout adjustment was used
- These limitations should be considered before using these models in clinical trial simulation
- For further investigation:
 - More comprehensive dropout model
 - Dose adjustments & non-adherence
 - Possibly misspecification of cure boundary
 - Covariance of inter-individual random effects

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