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.
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 μg/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
Methods

**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-binominal analysis in WinBUGS**

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**Viral response rate vs. time**

Study−level rates

Weighted rate (95% CI)

Viral response rate

0.0

0.2

0.4

0.6

0.8

1.0

0 20 40 ...

Viral response rate vs. time

Study−level rates

Weighted rate (95% CI)

Viral response rate

0.0

0.2

0.4

0.6

0.8

1.0

0 20 40 ...
### Simulated dropout due to insufficient response (%)

<table>
<thead>
<tr>
<th>Model</th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snoeck et. al.</td>
<td>22.5</td>
<td>11.9</td>
<td>34.4</td>
</tr>
<tr>
<td>Modified Dahari et. al.</td>
<td>35.2</td>
<td>1.2</td>
<td>36.4</td>
</tr>
</tbody>
</table>
Simulated viral load versus time (N=250)
Viral response rates versus time

Study-level rates  •  Weighted rate  •  Simulated

Time (weeks)

Dahari et. al.

Snoeck et. al.

Viral response rate

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Results

Viral response rates versus time

Study-level rates  Weighted rate  Simulated  Simulated – adj

Dahari et. al.

Snoeck et. al.

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HCV Model Evaluation

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Viral response rates versus time

Study-level rates

Weighted rate

Simulated

Simulated – adj

Dahari et. al.

Snoeck et. al.

Viral response rate

Time (weeks)

0 20 40 60
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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