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

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Objectives

The objective of this study was to compare both short- and long-term population-level viral responses 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 *in silico* populations of HCV genotype-1 infected patients (N=5000)
- Viral load profiles simulated in R using the `lsoda()` function in the `deSolve()` library
- Simulation Assumptions:
  1. Standard of care regimen:
     - peg-IFN-alfa-2a 180 μg per week + ribavirin 13 mg/kg/day x 48 weeks
  2. Viral load limit of detection: 100 copies/mL
  3. $ED50_{ifn}$, $ED50_{rbv}$, all between-subject variability parameters same for Snoeck and Dahari models
  4. Individual-level random effects uncorrelated; no residual unexplained variability in observations
- Subjects were dropped out from the study and assigned non-responder status according to virologic response at either 12 weeks (detectable viral load and $<$ 2-log drop from baseline viral load) or 24 weeks (detectable viral load) [9]
- Response rates (fraction of subjects with undetectable viral load and not dropped out) were calculated at 4, 12, 24, 48, and 72 weeks after starting treatment
- Meta Data Set
  - Simulated viral response rates were compared to response rates previously reported in clinical trials evaluating standard of care (peg-IFN-alfa-2a + ribavirin) therapy [12, 2, 4, 6, 9, 8, 1, 11, 7, 10]
  - Pooled response rates (across studies) were estimated at 4, 12, 24, 48 and 72 weeks using a beta-binomial model in WinBUGS, ignoring within-study correlation
  - Meta data was summarized by the 50, 2.5 and 97.5th percentile of the posterior distribution for time-specific viral response probability

HCV Dynamic Model Differential Equations as Published by Snoeck et. al. [13]

$$\frac{dT}{dt} = s + r \cdot T \cdot \left(1 - \frac{T+I}{T_{max}}\right) - d \cdot T - \beta \cdot V_I \cdot T \quad (1)$$

$$\frac{dI}{dt} = \beta \cdot V_I \cdot T + r \cdot I \cdot \left(1 - \frac{T+I}{T_{max}}\right) - \delta \cdot I \quad (2)$$

$$\frac{dV_I}{dt} = (1-\rho) \cdot (1-\varepsilon) \cdot (1 - \mathbb{I}^{I<CB}) \cdot p \cdot I - c \cdot V_I \quad (3)$$

$$\frac{dV_{NI}}{dt} = \rho \cdot (1-\varepsilon) \cdot (1 - \mathbb{I}^{I<CB}) \cdot p \cdot I - c \cdot V_{NI} \quad (4)$$

$$R_0 = \frac{p \cdot \beta \cdot s}{c \cdot \delta \cdot d}$$

$$\varepsilon = \frac{DOSE_{IFN}}{ED_{50_{IFN}} + DOSE_{IFN}}$$

$$\rho = \frac{DOSE_{RBV}}{ED_{50_{RBV}} + DOSE_{RBV}}$$

Table 1: *HCV Dynamic Model Parameters*

Parameter	Description	Units	SN	DH	IIV (%)
T_{max}	Maximum hepatocyte number	cells $\cdot$ mL^{-1}	18.5x10^6	1x10^7	
s	Hepatocyte production rate	cells$\cdot$ day^{-1}	61.7x10^3	2.6x10^3	
d	Hepatocyte death rate constant	day^{-1}	0.0033	0.0026	
R_0	Basic Reproductive Number	–	7.15	4.18	137
c	Viral elimination rate constant	day^{-1}	4.53	6	120
δ	Infected cell death rate constant	day^{-1}	0.139	0.26	58
p	Viral production rate constant	copies $\cdot$ cell^{-1} day^{-1}	25.1	2.9	
r	Hepatocyte regeneration rate constant	day^{-1}	0.00562	4.2	
IFN ED$_{50}$	peg-interferon ED$_{50}$	mcg$\cdot$week^{-1}	20.9	–	281
RBV ED$_{50}$	ribavirin ED$_{50}$	mg$\cdot$kg$^{-1}\cdot$day^{-1}	14.4	–	
k_{off}	Treatment effect decay	day^{-1}	0.0238	–	
CB	Cure boundary	cell $\cdot$ml^{-1}	1/13500	–	

SN = Snoeck et. al. model [13], DH = Dahari et. al. model [3]

Results

- 5-10% of simulated subjects had a baseline viral load that was BQL and were excluded from the data set prior to response rate determination.
- Overall dropout rate due to insufficient viral response was:
  - Snoeck: 34.4% (22.5% at 12 weeks and 11.9% at 24 weeks)
  - Dahari: 36.4% (35.2% at 12 weeks and 1.2% 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 4, 12, and 24 weeks, respectively

Figure 1: Viral Load Versus Time Simulated from Snoeck et. al. Model [13]

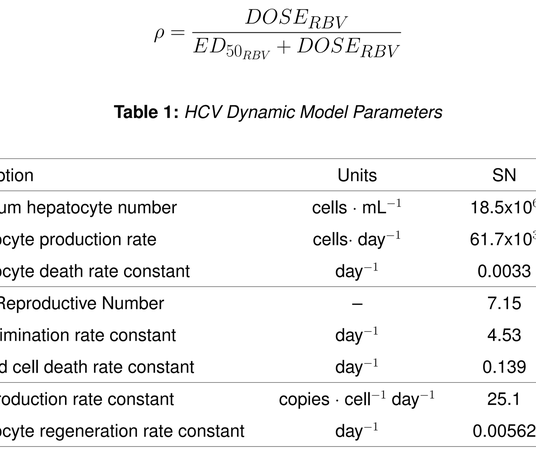
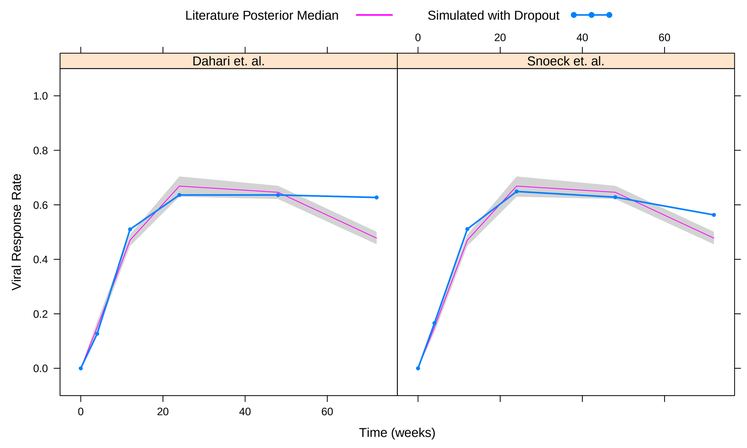


Table 2: *Comparison of Viral Response Rates for Simulated and Literature Data*

Week	Simulated Data		Meta Data Set	
	Model Source	Response Rate	Weighted Rate	N Subjects
4	DH	12.7	15.1	1888
	SN	17.0		
12	DH	50.1	47.1	2223
	SN	51.6		
24	DH	63.6	66.9	598
	SN	65.5		
48	DH	63.6	64.6	1506
	SN	63.5		
72	DH	62.7	47.8	1801
	SN	56.4		

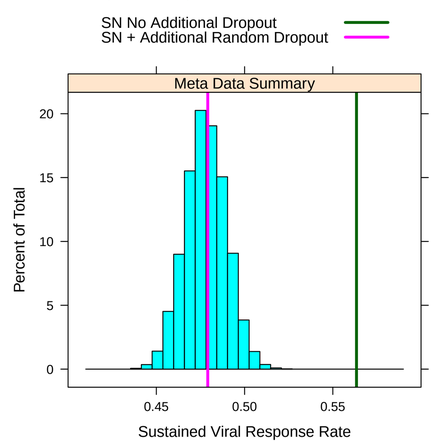
SN = Snoeck et. al. model [13], DH = Dahari et. al. model [3]

Figure 2: Model-predicted and Literature Response Rates Versus Time



Shaded area marks 95% credible interval for time-specific response probability.

Figure 3: Additional Random Dropout Helps SVR Prediction



A 9.8% random dropout (15% of those not already dropped out at end of treatment) was applied after week 48 and helped to match simulated and observed sustained viral response rates.

Conclusion

- Model-predicted viral response rates were similar for both models
- Simulated dropout rates due to insufficient viral response may be higher than observed rates [9, 5]
- SVR predictions were somewhat over-optimistic when dropout was based only on insufficient viral response at 12 and 24 weeks
- An additional $\sim$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 rate 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

[1] B R Bacon, M L Shiffman, J K Lim, A Berman, V K Rustgi, E B Keeffe, and STEALTH C-3 Investigators. Phase 2 randomized, double-blind, placebo-controlled study of nitazoxanide plus peginterferon and ribavirin in hcv genotype 1 naïve patients: Interim analysis shows increase in evr. *EASL 44th Annual Meeting*, 2009.

[2] Thomas Berg, Michael von Wagner, Samer Nasser, Christoph Sarrazin, Tobias Heintges, Tilman Gerlach, Peter Buggisch, Tobias Goeser, Jens Rasenack, Gerd R Pape, Wolfgang E Schmidt, Birgit Kallinowski, Hartwig Klinker, Ulrich Spengler, Peter Martus, Ulrich Alshuth, and Stefan Zeuzem. Extended treatment duration for hepatitis c virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology*, 130(4):1086–97, Apr 2006.

[3] Harel Dahari, Arthur Lo, Ruy M Ribeiro, and Alan S Perelson. Modeling hepatitis c virus dynamics: liver regeneration and critical drug efficacy. *J Theor Biol*, 247(2):371–81, Jul 2007.

[4] M. W. Fried, M. L. Shiffman, K. R. Reddy, C. Smith, G. Marinos, Jr. Goncales, F. L., D. Haussinger, M. Diago, G. Carosi, D. Dhumeaux, A. Craxi, A. Lin, J. Hoffman, and J. Yu. Peginterferon alfa-2a plus ribavirin for chronic hepatitis c virus infection. *The New England Journal of Medicine*, 347(13):975–982, 2002.

[5] Michael W Fried, Mitchell L Shiffman, K Rajender Reddy, Coleman Smith, George Marinos, Fernando L Gonçales, Jr, Dieter Häussinger, Moises Diago, Giampiero Carosi, Daniel Dhumeaux, Antonio Craxi, Amy Lin, Joseph Hoffman, and Jian Yu. Peginterferon alfa-2a plus ribavirin for chronic hepatitis c virus infection. *N Engl J Med*, 347(13):975–82, Sep 2002.

[6] Stephanos J Hadziyannis, Hoel Sette, Jr, Timothy R Morgan, Vijayan Balan, Moises Diago, Patrick Marcellin, Giuliano Ramadori, Henry Bodenheimer, Jr, David Bernstein, Mario Rizzetto, Stefan Zeuzem, Paul J Pockros, Amy Lin, Andrew M Ackrill, and PEGASYS International Study Group. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis c: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med*, 140(5):346–55, Mar 2004.

[7] Christophe Hézode, Nicole Forestier, Geoffrey Dusheiko, Peter Ferenci, Stanislas Pol, Tobias Goeser, Jean-Pierre Bronowicki, Marc Bourlière, Shahin Gharakhanian, Leif Bengtsson, Lindsay McNair, Shelley George, Tara Kieffer, Ann Kwong, Robert S Kauffman, John Alam, Jean-Michel Pawlotsky, Stefan Zeuzem, and PROVE2 Study Team. Telaprevir and peginterferon with or without ribavirin for chronic hcv infection. *N Engl J Med*, 360(18):1839–50, Apr 2009.

[8] John G McHutchison, Gregory T Everson, Stuart C Gordon, Ira M Jacobson, Mark Sulkowski, Robert Kauffman, Lindsay McNair, John Alam, Andrew J Muir, and PROVE1 Study Team. Telaprevir with peginterferon and ribavirin for chronic hcv genotype 1 infection. *N Engl J Med*, 360(18):1827–38, Apr 2009.

[9] John G McHutchison, Eric J Lawitz, Mitchell L Shiffman, Andrew J Muir, Greg W Galler, Jonathan McCone, Lisa M Nyberg, William M Lee, Reem H Ghalib, Eugene R Schiff, Joseph S Galati, Bruce R Bacon, Mitchell N Davis, Pabak Mukhopadhyay, Kenneth Koury, Stephanie Noviello, Lisa D Pedicone, Clifford A Brass, Janice K Albrecht, Mark S Sulkowski, and IDEAL Study Team. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis c infection. *N Engl J Med*, 361(6):580–93, Aug 2009.

[10] K R Reddy, M L Shiffman, M Rodriguez-Torres, D Abdurakhmanov, I Bakulin, G F Silva, H Cheinquer, M Rabbia, J Depamphilis, M McKenna, and S A Harrison. Standard versus higher induction doses of peginterferon alfa-2a (40kd) and/or higher ribavirin (rbv) in hcv g1 patients with high viral load and body weight 85 kg: Final results of the progress study. *60th Annual Meeting of the American Association for the Study of Liver Diseases*, 2009.

[11] Maria Grazia Rumi, Alessio Aghemo, Gian Maria Prati, Roberta D'Ambrosio, Maria Francesca Donato, Roberta Soffredini, Ersilio Del Ninno, Antonio Russo, and Massimo Colombo. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis c. *Gastroenterology*, 138(1):108–15, Jan 2010.

[12] José M Sánchez-Tapias, Moisés Diago, Pedro Escartín, Jaime Enríquez, Manuel Romero-Gómez, Rafael Bárcena, Javier Crespo, Raúl Andrade, Eva Martínez-Bauer, Ramón Pérez, Milagros Testillano, Ramón Planas, Ricard Solá, Manuel García-Bengoechea, Javier García-Samaniego, Miguel Muñoz-Sánchez, Ricardo Moreno-Otero, and TeraViC-4 Study Group. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis c virus rna at week 4 of treatment. *Gastroenterology*, 131(2):451–60, Aug 2006.

[13] E Snoeck, P Chanu, M Lavielle, P Jacqmin, E N Jonsson, K Jorga, T Goggin, J Grippo, N L Jumbe, and N Frey. A comprehensive hepatitis c viral kinetic model explaining cure. *Clin Pharmacol Ther*, 87(6):706–13, Jun 2010.

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