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To cite this version:
Eric Snoeck, Pascal Chanu, Marc Lavielle, Philippe Jacqmin, Niclas Jonsson, et al.. A Comprehensive Hepatitis C Viral Kinetic Model Explaining Cure. Clinical Pharmacology and Therapeutics, American Society for Clinical Pharmacology and Therapeutics, 2010, 87 (6), pp.706-713. <hal-00637434>

HAL Id: hal-00637434
https://hal.archives-ouvertes.fr/hal-00637434
Submitted on 2 Nov 2011

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A comprehensive Hepatitis C viral kinetic model explaining cure

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We propose a model that characterizes and links the complexity and diversity of clinically observed Hepatitis C viral kinetics to sustained virologic response (SVR, the primary clinical endpoint of Hepatitis C treatment defined as an undetectable viral load at 24 weeks after treatment completion) in Chronic Hepatitis C (CHC) patients treated with peginterferon \(\alpha\)-2a \(\pm\) ribavirin. New attributes of our Hepatitis C viral kinetic model are- i) the implementation of a cure/viral eradication boundary, ii) employing all HCV RNA measurements including those below the lower limit of quantification, and iii) implementation of a population modeling approach. The model demonstrated excellent positive (99.3\%) and negative (97.1\%) predictive values for SVR and high sensitivity (96.6\%) and specificity (99.4\%). The proposed viral kinetic model provides a framework for mechanistic exploration of treatment outcome, and permits evaluation of alternative CHC treatment options to ultimately develop and test hypotheses for personalizing treatments in this disease.
An estimated 170 million people or 2.1% of the world population are currently infected with hepatitis C virus (HCV), which is more than four times the number of people living with human immunodeficiency virus HIV (1). The current standard of care (SOC) for Chronic Hepatitis C (CHC) patients is the combination of pegylated interferon α with ribavirin (2,3). Successful HCV treatment outcome, i.e. sustained virologic response (SVR), is when a patient’s viral load is below the HCV RNA detection limit at a follow-up evaluation 24-weeks following treatment completion. SVR rates of up to 66% have been obtained with the optimal regimen of peginterferon α-2a plus ribavirin in treatment-naïve patients in large, randomized, multicentre trials (4,5). Patients infected with the more difficult to treat HCV genotype 1 (G1), which represent about 70% of CHC patients in the US (6), are less likely to achieve an SVR than genotype non-1 (Gn1) infected patients. Approximately 50% of HCV G1 infected patients achieved an SVR when treated with peginterferon α-2a plus ribavirin, whereas approximately 80% of HCV Gm1-infected patients achieved an SVR despite receiving a shorter treatment duration and a lower ribavirin dose (5). Thus, HCV patients represent a population with continued unmet medical need, having the potential to achieve a higher SVR rate through optimized treatment approaches.

Modeling hepatitis C virus (HCV) dynamics during therapy has led to important insights into the life cycle of HCV elucidating the kinetic parameters governing viral infection and hepatocyte death, the antiviral effects of interferons, and how ribavirin impacts HCV treatment (7). Models of HCV kinetics have provided a means to compare different treatment regimens and outcomes in different patient populations (8). A model of HCV infection was originally proposed by Neumann et al. (9) who adapted a model of HIV infection (10,11). The Neumann model adequately describes typical short-term...
therapy outcome characterized by an initial rapid viral decline followed by a second
slower decline until HCV RNA becomes undetectable (12,13). This model has therefore
been frequently used to describe viral load profiles after short-term treatment (8,14,15).
However, after current long-term SOC treatment, the virus is not eradicated in all CHC
patients (5). In the patients who do not achieve SVR (i.e. the virus is not eradicated),
viral load either rebounds to pretreatment levels during therapy (breakthrough), or
returns to pretreatment levels upon cessation of therapy (relapse) (13). These two
phenomena, and crucially, an SVR cannot be described by the Neumann model (13),
and are the primary reason why early viral response does not uniformly predict the
clinical endpoint. Finally, and most importantly, previous analyses have used a naïve
method of handling the HCV RNA measurements below the lower limit of
quantification (LLOQ) by omission of all these measurements even though these values
contain critical information regarding long-term treatment outcome.

In this communication, we propose a novel approach of modelling the viral kinetics in
Hepatitis C. Firstly, a non-linear mixed effects model was developed by maximum
likelihood estimation (MLE) of the parameters using the extended stochastic
approximation expectation-maximization (SAEM) algorithm as implemented in the
MONOLIX software (16). Individual long-term HCV kinetic profiles of 2,100 CHC
patients treated with peginterferon α-2a alone or in combination with ribavirin using a
wide spectrum of dosing regimens were simultaneously described. Secondly, HCV
RNA measurements below the LLOQ were included. The proposed model permits the
distinction between SVR and LLOQ by including censored data residing between the
HCV RNA LLOQ and the irrevocable lower boundary of zero. Thirdly, cure or
complete virion eradication was determined from viral kinetics by implementation of a
viral eradication boundary. At the time point at which treatment drives the system to less than one infected hepatocyte, the production of virions was set to zero. Modeling results characterizing differences between patients having an SVR and those failing treatment were explored in order to derive mechanistic hypotheses underpinning treatment failure or success.

RESULTS
Parameters of the model were estimated with good precision (Table 1). The typical value of the basic reproduction number $R_0$ was estimated to be 7.2 with an inter-individual variability (IIV) of 137% CV. The relatively large IIV likely reflects the large intrinsic biological difference in CHC disease. $R_0$ represents relative drug-effect distance from the treatment intervention goal, which is to drive the reproduction number during treatment ($R_T$) below 1 (Supplementary text note 2 online), in order to increase the likelihood of attaining SVR (i.e. cure, defined as I < 1 infected hepatocyte). Inspection of the individual parameter estimates in patients experiencing a breakthrough during therapy indeed showed that the administered drug therapy failed to decrease the reproduction number ($R_T$) below 1 (17,18). The maximum hepatocyte proliferation rate ($r$) was 0.00562 day$^{-1}$, and simulations based on this $r$ revealed that the predicted liver regeneration matched well with the increase in original liver volume in 51 donors as measured 1 year after providing right-lobe liver grafts [Supplementary text note 3 online (19)]. The typical value of the virion production rate $p$ was 25.1 virions·day$^{-1}$ and the free virion clearance rate $c$ was estimated to be 4.53 day$^{-1}$, corresponding to a free virion half-life of 3.7 hours. This half-life lies within the previously reported range of 1.5-4.6 hours (12,13). Free virion clearance rate was found not to be influenced by HCV
genotype. In contrast, the infected cell death rate ($\delta$) appeared to be dependent on HCV genotype, and the typical value was estimated to be 0.139 day$^{-1}$ in genotype-1 infected patients and 0.192 day$^{-1}$ in patients infected with HCV G1n (Table 1). These estimates are in line with previously reported values of $\delta$ (20). The higher $\delta$ in HCV G1n infected patients may indicate an enhanced immunological response and is in line with the previous finding that a fast viral decay early in treatment correlates with SVR (20). Also, the typical value of the $ED_{50,\text{peg}}$ was found to be lower in HCV G1n patients as compared to patients infected with HCV G1, confirming the higher antiviral effectiveness of peginterferon $\alpha$-2a in blocking virion production in G1n patients [Table 1 and (20)]. The $ED_{50,\text{peg}}$ was estimated to be 14.4 mg·kg$^{-1}$·day$^{-1}$, which corresponds to rendering a fraction of 40-60% of the virions non-infectious for a standard ribavirin treatment of 1,000/1,200 mg per day (see equation 6). The anti-viral effect decay constant ($K$) was estimated to be 0.0238 day$^{-1}$, which corresponds to a half-life of approximately 29 days. As the terminal half-life after multiple dosing of peginterferon $\alpha$-2a is approximately 160 h and that of ribavirin is approximately 12 days (21), the anti-viral effect decay constant may describe both pharmacokinetic and pharmacodynamic processes. Finally, the variance of the residual error ($\sigma^2$) was estimated to be 0.260. This residual error is relatively high but not uncommon for viral kinetic models as a $\sigma^2$ of 0.38 was obtained previously in a similar analysis of HIV viral load data (22).

**Model evaluation and qualification**

The goodness of fit assessment revealed that the individual viral load profiles are well described by the model (Supplementary text note 4 online). Population based
diagnostics were also used, but are not easily interpretable unless simulated reference graphs from the true model are used for comparison [Supplementary text note 4 online (23)]. A selection of 12 individual viral load profiles shows that the HCV viral kinetic model is able to not only describe the initial decreases in viral load over the first month, but also the typical phenomena observed after longer-term therapy (Figure 3). The model provided satisfactory positive (99.3%) and negative (97.1%) predictive values for SVR combined with a high sensitivity (96.6%) and specificity (99.4%) [Supplementary text note 5 online].

The predictive performance of the model was assessed by a model evaluation procedure using the design and data of a large clinical trial not included in the model building dataset (4). The model was successfully qualified for further simulations as the predicted range of SVR rate in HCV G1 and Gn1 infected patients receiving 48 weeks of treatment with peginterferon α-2a alone or in combination with ribavirin matched well with the observed SVR rate in this study (Figure 5).

Discussion

The multi-dimensional interactions between HCV virus, host and drug are highly non-linear and equilibrium outcomes quickly become counter-intuitive (24). Here, we propose a population approach using MLE by the extended SAEM algorithm as implemented in the MONOLIX software (16), to simultaneously describe individual long-term HCV kinetic profiles of 2,100 CHC patients treated with peginterferon α-2a alone or in combination with ribavirin. The four ordinary differential equations (ODE’s) of the HCV viral kinetic model (equations 1-4) were implemented in MONOLIX. HCV viral kinetic models including ODE’s have been previously used for exploratory
simulations (17,25), however not for simultaneously fitting the complexity and diversity of clinically observed HCV viral kinetics.

The proposed model addresses the host-virus-drug interaction by advancing previously known and novel ideas from a population perspective, simultaneously analyzing a wide spectrum of treatment regimens (drug combinations, drug doses, schedule and treatment durations), incorporating left-censored data previously largely excluded from analysis, and implementing a viral eradication *cure* boundary to link viral kinetics to clinical outcome (i.e. SVR). The final viral kinetic model was qualified using internal and external datasets, including HCV G1 and Gn1 infected patients, and demonstrated positive and negative predictive values as well as sensitivity and specificity exceeding 96%.

In clinical practice, milestone target treatment strategies, i.e., rapid virologic response (RVR)- defined as attainment of undetectable HCV RNA level by week 4 of therapy (26,27), or early virologic response (EVR)- defined ≥ 2 log reduction or undetectable serum HCV RNA at week 12 of treatment, have been proposed to optimize SVR rates by modifying treatment duration. However, these early treatment response landmarks (regardless of time point) do not uniformly predict SVR because viral load either rebounds to pretreatment levels during therapy (*breakthrough*), or returns to pretreatment levels upon cessation of therapy (*relapse*). This observations leads to two conclusions, (i) the relationship between RVR/EVR and SVR is correlative but not prescriptive, and (ii) excluding HCV RNA measurements below the LLOQ (i.e., left-censoring) likely biases SVR predictions. An extension of the SAEM algorithm as implemented in the *MONOLIX* software handles left-censored data in nonlinear mixed-effects models with computational efficiency (22). Comparison with classical methods
of handling missing data shows that the extended SAEM algorithm is less biased than excluding subjects with censored measurements, omission of all censored data points, and/or imputation to half the quantification limit for the first point below the LLOQ with omission of subsequent missing data (28). Furthermore, the extended SAEM algorithm has been demonstrated to be more efficient and/or less biased than linearization or Monte Carlo approximation of the expectation step applied to censored values (22).

The implementation of the cure boundary in the viral kinetic model is physiologically based and consistent with the primary goal of HCV therapy, which is to completely eradicate the virus. The final viral kinetic model was implemented as a two state system. The off state (null virion production) was triggered when there was less than one infected hepatocyte in the total plasma and extracellular fluid volume of distribution thereby resulting in cure/SVR. The on state (constitutive virion production), inadvertently returns the patient to full blown disease when even a minute fraction of one infected hepatocyte remains.

A comparison of the individual parameter estimates between patients with and without an SVR reveals that $R_0$ and $ED_{50,PEG}$ are generally lower in SVR patients (Figure 4). A relatively low $R_0$ prior to treatment and a relatively high inhibition of the virion production increase the likelihood of $R_T < 1$ during treatment and will thus increase the likelihood of SVR.

Inspection of the individual parameter estimates in patients experiencing a breakthrough during therapy indeed showed that the administered drug therapy failed to decrease the $R_T$ below 1 (17,18). According to our modeling assumptions, a treatment with either higher doses or a combination treatment with new drugs may be an option in these
patients in order to drive $R_T$ below 1. The conditional explanation in patients relapsing
after the end of treatment may be twofold: i) on the one hand, relapsing patients may
have had a $R_T < 1$ during treatment, but were not treated long enough to cross the cure
boundary of $I < 1$ cell, so that the viral load quickly returned back to baseline at the end
of therapy, or ii) drug therapy may have failed to decrease the $R_T$ below 1 (inadequate
efficacy). Extended treatment duration at the same drug combination, dose and schedule
in relapsing patients may therefore be an option in the former situation but not in the
latter. Based on these hypotheses, individual treatments may be optimized when the
individual $R_0$ and inhibition of the virion production are pre-determined or determined
early at treatment onset. The interplay between treatment duration, dose and schedule,
and/or sensitivity of hitting the cure boundary after high dose induction is yet to be fully
elucidated.

In our model-based analysis, the free virion clearance rate ($c$) did not appear to be a
prognostic factor for SVR (Figure 4), whereas the death rate of infected cells ($\delta$) was
found to be generally higher in SVR patients indicating these patients may have an
enhanced immunological response and thus a higher likelihood of viral eradication.

Our proposed viral kinetic model is a simplification of the complex interaction between
host, infected hepatocytes, virus, and mechanisms of drug action and required fixing of
several liver physiology parameters to biologically justifiable values. Furthermore, the
combination of peginterferon $\alpha$-2a and ribavirin is assumed to inhibit in a multiplicative
way the virion production ($p$) according to $E_{\text{max}}$ dose-response relationships. While
some confidence in the predictive performance of the model is derived from the
qualification exercise described above, complete understanding of the implications of
these assumptions is not fully understood and should be further explored, particularly in
the case where the model would be used to explore the efficacy of new drugs in combination with SOC. Another limitation of our current model is the fact that dose was used as the perturbation to the system. Since HCV SOC pharmacotherapy has been established through empirical study over a decade, investigation of schedule dependence was not considered as primary to our objectives. This implies that a pharmacokinetic model component will have to be added to the current model for the evaluation of schedule dependence and/or adherence, especially for drugs with shorter pharmacokinetic half-lives that are being developed.

In summary, our population HCV viral kinetic model was able to adequately describe all individual long-term viral load profiles of 2,100 CHC patients receiving chronic treatment of peginterferon α-2a alone or in combination with ribavirin. The model provides new insights and explanations for typical phenomena observed in the clinic such as breakthrough during therapy, relapse after stopping therapy and cure (or SVR). Simulations based on our model may help to better understand current treatment success and failure, and can also be used to predict and evaluate the efficacy of alternative treatment options (e.g. alternative doses, durations and, with additional assumptions-new drug combinations) in the overall CHC patient population. This will be described in a follow-up communication. The proposed viral kinetic model provides a framework for developing and testing hypotheses for evaluating new antiviral agents and personalizing CHC treatments that would ultimately need to be validated in well designed clinical trials.

METHODS

Patients and Data
Data from one phase-II study and four phase-III studies of peginterferon α-2a (40KD) (Pegasys®) alone or in combination with ribavirin (Copegus®) were pooled. All patients were required to have histologically and serologically proven CHC. The complete inclusion and exclusion criteria, study design, and primary results have been published elsewhere (5, 29-32). A total of 2,100 CHC patients were included in the final database.

Serum HCV RNA (COBAS AMPLICOR™ HCV Test, version 2.0) was measured at specific time points during treatment and during the 24-week untreated follow-up period. All available 21,284 HCV RNA measurements, of which 59% were below the LLOQ, were modeled by accounting for the left-censoring in the analysis. The LLOQ of the two different assays used were 50 IU/mL and 600 IU/mL (33).

HCV viral kinetic model

The viral kinetic model (equations 1-4) extends the original Neumann (9) model, to include important contributions by Dahari et al. (density dependent proliferation of hepatocytes [r], 17) and Pomfret et al. (hepatocyte intrinsic production, 19). Treatment effect of peginterferon α-2a [ε] and the effect of ribavirin rendering a fraction of newly produced virions non-infectious [ρ] (7) was implemented on the virion production rate (ρ). The model structure of the viral kinetic model (Figure 1) is described by the following mass balance equations:

\[
\frac{dT}{dt} = s + r \cdot T \cdot \left(1 - \frac{T + I}{T_{\text{max}}}\right) - d \cdot T - \beta \cdot V_t \cdot T
\]

\[
\frac{dI}{dt} = \beta \cdot V_t \cdot T + r \cdot I \cdot \left(1 - \frac{T + I}{T_{\text{max}}}\right) - \delta \cdot I
\]

\[
\frac{dV_t}{dt} = (1 - \rho) \cdot (1 - \varepsilon) \cdot p \cdot I - c \cdot V_t
\]
\[
\frac{dV_{NI}}{dt} = \rho \cdot (1 - \varepsilon) \cdot p \cdot I - c \cdot V_{NI}
\]

(4)

where, infectious HCV virions \((V_I)\) infect target cells (uninfected hepatocytes) \([T]\), creating productively infected cells \((I)\) at a rate \(\beta \cdot V_I T\). Uninfected hepatocytes are produced at rate \(s\) and die at rate \(d\). Infected hepatocytes die at rate \(\delta\). Similar to Dixit et al. (7), it is assumed that infectious \((V_I)\) and non-infectious \((V_{NI})\) virions are produced from infected hepatocytes at rate \(p\) and cleared at rate \(c\). The measured viral load \((V)\) is expressed in IU/mL, representing the sum of infectious and non-infectious virions \(V = V_I + V_{NI}\). The model was further extended with \(E_{max}\) dose-response models describing the dose-dependent effects of peginterferon \(\alpha-2a\) and ribavirin:

\[
\varepsilon = \frac{Dose_{PEG}}{ED_{50_{PEG}} + Dose_{PEG}}
\]

(5)

\[
\rho = \frac{Dose_{RBV}}{ED_{50_{RBV}} + Dose_{RBV}}
\]

(6)

where \(Dose_{PEG}\) is the weekly subcutaneous dose of peginterferon \(\alpha-2a\) and \(ED_{50_{PEG}}\) is the estimated weekly dose of peginterferon \(\alpha-2a\) resulting in a 50% inhibition of the virion production. Similarly, \(Dose_{RBV}\) is the daily dose of ribavirin per kg body weight and \(ED_{50_{RBV}}\) is the estimated daily dose in mg/kg rendering 50% of the virions non-infectious. \(Dose_{RBV}\) and \(ED_{50_{RBV}}\) were expressed as mg/kg as ribavirin is dosed by body weight and ribavirin in mg/kg has been previously found to be a prognostic factor for SVR (34).

The implementation of a cure/viral eradication boundary represents a milestone contribution in enabling linking the complexity and diversity of clinically observed Hepatitis C viral kinetics to SVR. The cure boundary was based on the assumption that...
virion production ($p$) should cease when all infected cells are cleared, i.e., when there is less than 1 infected cell in the total plasma and extracellular fluid volume of approximately $13.5 \cdot 10^3$ mL. At the time point at which treatment anti-viral effect drove the system to less than one infected hepatocyte, the virion production $p$ was set to zero (off state), resulting in a model cure/SVR [Supplementary text note 1 online (35)]. Exploratory simulations without this additional model component of cure predicted rapid viral load return to baseline in all CHC patients when treatment was stopped [Supplementary text note 1 online (35)], while in reality the virus is eradicated after the current standard treatment of care in the majority of G1 infected patients and approximately half of the HCV G1 patients and approximately (5).

A fundamental parameter of the viral kinetic model is the estimated basic reproduction number ($R_0$) [Supplementary text note 2 online (18)]. Previously, it was shown that the reproduction number in the presence of an inhibitor ($R_T$) is (36):

$$ R_T = R_0 \cdot (1 - \epsilon_T) $$

(8)

where $\epsilon_T$ is the total treatment-induced inhibition of the virion production. As infection in the presence of an inhibitor has been shown to be cleared when $R_T < 1$ (36), $\epsilon_T$ combined with $R_0$ are thus important predictors for a successful drug therapy. For this reason, our model was parameterized in terms of $R_0$, by using the following equation for $R_0$ (18):

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

(9)

Finally, drug-effect after stopping treatment was described by an exponential decay function ($e^{-Kt}$, Figure 2), where $K$ is the estimated antiviral-effect decay constant and $t$ the time from the end of treatment. Without the inclusion of this exponential decay
function, the viral load in relapsing patients after stopping therapy appeared to return too rapidly to pre-treatment values.

**Model assumptions**

Currently available data did not allow the estimation of all parameters of the declared viral kinetic model due to issues of mathematical identifiability. For this reason, a number of system/physiological parameters were fixed to biologically justifiable values. The maximum number of hepatocytes present in an individual liver was assumed to be $2.50 \times 10^{11}$ hepatocytes (37). As HCV RNA is distributed in plasma and extracellular fluids with a volume of approximately $13.5 \times 10^3$ mL (38), the maximum number of hepatocytes ($T_{\text{max}}$) was assumed to be $18.5 \times 10^6$ cells·mL$^{-1}$ (12). Assuming a hepatocyte turnover in a healthy liver of 300 days (39), the death rate of target cells ($d$) was set to $1/300$ day$^{-1}$, and therefrom ($T_{\text{max}} \cdot d$) the production of new hepatocytes in the absence of liver disease ($s$) could be assumed to be $61.7 \times 10^3$ cells·mL$^{-1}$ days$^{-1}$ (12). Estimated proliferation rates were set to be equal across infected and uninfected hepatocytes due to a lack of direct information to the contrary.

Non-linear mixed effects models comprise of a combination of fixed and random effects. Individual parameters ($\text{PAR}_i$) in such a model are assumed to be log-normally distributed and can be described by:

$$\text{PAR}_i = \theta \cdot e^{\eta_i}$$

(7)

where, subscript $i$ denotes individual, the fixed effects parameter $\theta$ represents the median (typical) value of the parameter in the population, and $\eta_i$ is the random effect accounting for the individual difference from the typical value. The $\eta_i$ values are assumed to be normally distributed in the population with a mean of zero and an
estimated variance of $\omega^2$. Individual parameter estimates are used to predict the viral load in an individual $i$ at a certain point in time $j$ ($V_{pred,ij}$). The measured viral load data ($V_{obs,ij}$) were log$_{10}$-transformed for the analysis in order to be able to handle the wide range of viral load observations, and an additive residual error model was used for the log$_{10}$-transformed viral load data:

$$\log_{10} V_{obs,ij} = \log_{10} V_{pred,ij} + \epsilon_{ij}$$

(8)

The $\epsilon_{ij}$ values are assumed to be normally distributed with a mean of zero and an estimated variance $\sigma^2$. The $\omega^2$ quantifies the inter-individual variability (IIV) and the $\sigma^2$ quantifies the residual variability.

Estimated fixed effects parameters were $R_0$, $p$, $c$, $\delta$, liver proliferation rate $r$ [Supplementary text note 3 online (17)], $ED_{50,rec}$, $ED_{50,av}$ and $K$. IIV was incorporated on the parameters $R_0$, $c$, $\delta$ and $ED_{50,rec}$.

Parameter estimation

Population parameters of our HCV viral kinetic model were estimated using MLE by the SAEM algorithm for hierarchical nonlinear mixed effects model analysis (40,41). Individual parameters were obtained by computing for each individual patient the so-called Maximum A Posteriori (MAP) estimate, which maximizes the conditional distribution of the individual parameters using the MLE of the population parameters computed previously with the SAEM algorithm (40). SAEM is a powerful algorithm for MLE in complex models, including dynamic models defined by a system of ODE’s. Furthermore, the left-censored data are properly handled by the extended SAEM algorithm for MLE as described by Samson et al. (22). The extended SAEM algorithm...
for MLE is implemented in the *MONOLIX* software, available on the author’s website (16). We used version 2.4 of *MONOLIX*.

**Model evaluation and qualification**

Goodness of fit was assessed by the method of simulating from the final model and re-fitting (23). Since by definition, the proposed model does not characterize SVR directly, but SVR is derived from crossing the model *cure* boundary, the predictive performance of the model in correctly classifying patients into SVR or non-SVR, which is considered one of the core utilities of the model, could be assessed by calculating the sensitivity and specificity (42,43) without confounding bias. The predictive performance of the model was assessed by a model evaluation procedure using the design and data of a large clinical trial not included in the model building dataset. In this trial, 180 µg peginterferon α-2a was administered once weekly for 48 weeks, alone or in combination with daily 1,000 or 1,200 mg ribavirin (4). Dropout rates in the simulated cohort were matched to historical data by random assignment and defining dropouts as non-SVR. The uncertainty of the observed SVR rates was quantified by 400 bootstrap samples and compared to observed SVR rates in the trial.

**ACKNOWLEDGMENTS**

We wish to pay tribute to the 2,100 anonymized patients whose data is included in this analysis, physicians and nurses who took care of them, and the Pegasys® Life Cycle Team for their vision and support in the development of this model. We thank Frank Duff, Annabelle Lemenuel and Rohit Kulkarni for scientific input and editorial
assistance, and Sharon Lim and Marlene Hering for help in the preparation of this manuscript.

Financial disclosure: P. Chanu, K. Jorga, T. Goggin, J. Grippo, N. L. Jumbe, and N. Frey are F. Hoffman-La Roche Ltd employees. E. Snoeck, P. Jacqmin, and N. Jonsson are compensated F. Hoffman-La Roche Ltd. consultants. M. Lavielle is the developer of MONOLIX and has no conflict of interest.
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**Figure 1.** Representation of the extended HCV viral kinetic model. Infectious HCV virions ($V_I$) infect target cells ($T$), creating productively infected hepatocytes ($I$). Uninfected hepatocytes ($T$) are produced at rate $s$ and die at rate $d$. Infected hepatocytes die at rate $\delta$. A density dependent proliferation of hepatocytes ($r$) is assumed. Infectious ($V_I$) and non-infectious ($V_{NI}$) virions are produced at rate $p$ and cleared at rate $c$. Peginterferon $\alpha$-2a dose-dependently inhibits the production of new virions ($\varepsilon$), and ribavirin dose-dependently renders a fraction of newly produced virions non-infectious ($\rho$). SVR, defined as an undetectable viral load at 24 weeks after treatment completion, is the primary clinical endpoint desired to be predicted in the treatment of Hepatitis C.
Figure 2. The viral kinetic model characterizes the complexity and diversity of clinically observed HCV viral kinetics in Hepatitis C virus patients treated with peginterferon α-2a alone or in combination with ribavirin, and links the kinetics to clinical outcome. This is achieved by the implementation of a viral eradication cure boundary and incorporation of left-censored data, previously largely excluded from analysis, from simultaneous analysis of a wide spectrum of peginterferon α-2a ± ribavirin treatment regimens from 2,100 patients. RVR and EVR are rapid virologic response and early virologic response, respectively.
Figure 3. Observed and model-predicted long-term viral load profiles in 12 representative CHC patients. Solid lines are the fits of the model to the individual viral load data which are either detectable (closed circles) or below the LLOQ of 50 IU/mL (closed triangles). Dotted horizontal lines show the LLOQ of the assay. Dotted vertical lines indicate the end of treatment. Our HCV viral kinetic model is able to describe all the typical phenomena observed after long-term therapy such as null response (no change in viral load), partial virologic response (initial decrease followed by increase during treatment), breakthrough during therapy (non-detectable viral load followed by increase during treatment), relapse after therapy (non-detectable viral load at the end of therapy followed by an increase during the treatment-free follow-up period), and SVR (non-detectable viral load at 24 weeks after end of therapy).
**Figure 4.** Boxplots of the individual HCV viral kinetic model parameters as split by patient outcome (i.e. SVR (n = 974) versus non-SVR (n = 1,126) patients). The basic reproduction number ($R_0$) is generally higher and more variable in patients without an SVR (A). The free virion clearance rate ($c$) is not different between patients with and without an SVR (B). The infected cell death rate ($\delta$) is generally higher in patients with an SVR (C), and the effectiveness of peginterferon $\alpha$-2a in inhibiting the production of new virions is generally higher in patients with an SVR (D).
Figure 5. Observed (black vertical lines) and model predicted SVR rates (transparent histogram) of the phase-III study by Fried et al. (4), investigating 180 µg peginterferon α-2a once weekly for 48 weeks given alone or in combination with daily 1,000 or 1,200 mg ribavirin. Dropouts have been taken into account in the predictions by randomly assigning patients as dropout and defining them as non-SVR. The uncertainty of the observed SVR rates was quantified by 400 bootstrap samples (grey histograms). The observed SVR rate in 297 HCV G1 patients receiving combination therapy falls within the range of model predicted SVR rates (A). The observed SVR rate in 154 HCV G1 patients receiving combination therapy also falls within the range of model predicted SVR rates (B). The observed SVR rate in 143 HCV G1 patients receiving monotherapy of peginterferon α-2a falls within the range of model predicted SVR rates (C). Finally, also the observed SVR rate in 77 HCV G1 patients receiving monotherapy of peginterferon α-2a falls within the range of model predicted SVR rates (D).
Table 1. Population parameters of the HCV viral kinetic model fitted to the individual long-term viral load profiles of 2,100 CHC patients receiving chronic treatment of peginterferon α-2a alone or in combination with ribavirin*. The upper part of the table represents the fixed parameters according to our assumptions, the middle part are system-specific parameters and the lower part are the drug-specific parameters. The SE reflects the precision of the estimated parameters and IIV represents the inter-individual variability (Supplementary text note 5 online).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Unit</th>
<th>Typical value</th>
<th>SE (%CV)***</th>
<th>IIV (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_{\text{max}} )</td>
<td>Total amount of hepatocytes per mL</td>
<td>hepatocytes·mL(^{-1})</td>
<td>18.5·10^6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( s )</td>
<td>Hepatocyte production rate</td>
<td>hepatocytes·mL(^{-1})·day(^{-1})</td>
<td>61.7·10^3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( d )</td>
<td>Hepatocyte death rate constant</td>
<td>day(^{-1})</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( r )</td>
<td>Hepatocyte proliferation rate constant</td>
<td>day(^{-1})</td>
<td>0.00562 22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( R_0 )****</td>
<td>Basic reproductive number</td>
<td></td>
<td>7.15 9 137</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p )</td>
<td>Virion production rate</td>
<td>virions·hepatocyte(^{-1})·day(^{-1})</td>
<td>25.1 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( c )</td>
<td>Virion elimination rate constant</td>
<td>day(^{-1})</td>
<td>4.53 15 120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \delta_{\text{HCV non-1}} )</td>
<td>Infected cell death rate constant (HCVGn1)</td>
<td>day(^{-1})</td>
<td>0.192 16 58*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \delta_{\text{HCV-1}} )</td>
<td>Infected cell death rate constant (HCV G1)</td>
<td>day(^{-1})</td>
<td>0.139 3 58*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( ED_{50,\text{HCV non-1}} )</td>
<td>( ED_{50,\text{HCV Gn1}} ) of peginterferon α-2a (HCV Gn1)</td>
<td>µg·week(^{-1})</td>
<td>1.19 17 281*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( ED_{50,\text{HCV-1}} )</td>
<td>( ED_{50,\text{HCV genotype-1}} ) of peginterferon α-2a (HCV genotype-1)</td>
<td>µg·week(^{-1})</td>
<td>20.9 10 281*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( ED_{50,\text{RBV}} )</td>
<td>( ED_{50,\text{ribavirin}} ) of ribavirin</td>
<td>mg·kg(^{-1})·day(^{-1})</td>
<td>14.4 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( K )</td>
<td>Anti-viral effect decay constant</td>
<td>day(^{-1})</td>
<td>0.0238 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \sigma^2 )</td>
<td>Residual error</td>
<td></td>
<td>0.260 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 47% received monotherapy of peginterferon α-2a at a weekly subcutaneous dose of 45 µg (20 patients), 90 µg (114 patients), 135 µg (210 patients), 180 µg (596 patients) or 270 µg (38 patients). The CHC patients receiving combination therapy were administered a subcutaneous dose of 180 µg/week peginterferon α-2a and a daily dose of 800 mg or 1,000/1,200 mg ribavirin. Almost all patients (93%) received 24 weeks of treatment or more, and 61% of CHC patients received 48 weeks of treatment or more.

** Assumed to be similar between HCV genotype-1 and non-1 infected patients.

*** As \( T_{\text{max}} \), \( s \) and \( d \) were fixed, no SE is provided.

**** \( R_0 \) is defined as the number of newly infected cells that arise from one infected cell when almost all cells are uninfected and has therefore no units.
Supplementary text note 1: additional model component for HCV virion eradication

Exploratory simulations were undertaken based on the HCV viral kinetic model as described by equations 1-6 of the manuscript. An evaluation of the simulated viral load profiles of the CHC patient population revealed that the viral load in all patients rapidly returned back to baseline within approximately 4 to 8 weeks after stopping the 48-week treatment (Figure S1). This implies that an SVR cannot be described without adding a model component for HCV virion eradication. A subsequent simulation based on the same model where only one infected cell (I) remained at the end of treatment showed again a rapid return to baseline within approximately 4 weeks (Figure S2). As the virion production $p$ should cease when all infected hepatocytes are cleared, parameter $p$ was set to zero (off state) during the model fitting procedure when the number of infected hepatocytes crossed the $< 1$ cell or $< 1/13500$ cells·mL$^{-1}$ cure boundary condition.

Supplementary text note 2: basic reproduction number ($R_0$)

The basic reproduction number of an infection is defined as the number of newly infected hepatocytes that arise from one infected cell when almost all cells are infected, i.e. prior to treatment initiation ($SI$). When $R_0 < 1$, the infection will be spontaneously cleared in the long run. But if $R_0 > 1$, the infection will be able to expand. When $R_0 = 1$, the infection will not be cleared or expand but remain at some quasi-disease equilibrium. Using a simple PK-PD model for proliferative systems, it can be shown that the reproduction number in the presence of an inhibitor of the virion production ($R_T$) is (S2):

$$R_T = R_0 \cdot (1 - \varepsilon_T)$$

(1)
where $\varepsilon_t$ is the total treatment-induced inhibition of the virion production. The infection in the presence of an inhibitor will die out in case $R_T < 1$ (S2). $R_0$ thus carries information on the status of infection, whereas $R_T$ carries information about treatment effect and the likelihood of cure.

Simulations based on our HCV viral kinetic model confirmed the previous findings based on the simple PK-PD model for proliferative systems (Figure S3). The total drug effectiveness $\varepsilon_t$ combined with $R_0$ are thus important predictors for successful drug therapy. For this reason, our model was parameterized in terms of $R_0$, by using the following equation for $R_0$ (S3):

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

(2)

In our model, the parameters $d$ and $s$ are assumed to be respectively $1/300$ day$^{-1}$ and $61.7 \cdot 10^3$ cells$\cdot$mL$^{-1}$ days$^{-1}$, whereas $R_0$, $c$, $p$ and $\delta$ are estimated so that the de novo infection rate constant $\beta$ can be calculated.

**Supplementary text note 3: liver proliferation rate ($r$)**

The liver is a unique organ as it self-heals by regeneration as opposed to repair. The exact cellular and molecular mechanisms of liver regeneration are still not yet fully understood (S4,S5). The Neumann HCV viral kinetic model was extended with a density-dependent liver proliferation term to describe the liver regeneration (S6). For liver regeneration in healthy liver donors, the liver regrowth can be described in a similar way:

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

(3)

$T$ represents the number of hepatocytes in cells$\cdot$mL$^{-1}$. The maximum number of hepatocytes present in an individual liver ($T_{max}$) is assumed to be $18.5 \cdot 10^6$ cells$\cdot$mL$^{-1}$. 
The death rate of hepatocytes \( (d) \) is assumed to be \( \frac{1}{300} \) day\(^{-1} \), and the production of new hepatocytes \( (s) \) is thus \( 6.17 \times 10^3 \) cells\( \cdot \)mL\(^{-1} \) days\(^{-1} \) from steady-state assumptions. Simulations of the liver regeneration based on the above mentioned equation and the model estimated a maximum liver proliferation rate \( (r) \) of \( 0.006 \) day\(^{-1} \), and also revealed a rapid initial liver regrowth (Figure S4). For a donor remnant liver volume of 50\%, the total liver volume was predicted to be approximately 89\% after 360 days. This predicted total liver volume matched well with the increase in original liver volume as measured over a 1-year time period in 51 donors who provided right-lobe liver grafts (S7).

**Supplementary text note 4: goodness of fit assessment**

As anticipated, a diagnostic plot of the observed viral load values (DV) *versus* the population predictions (PRED) [Figure S5] is neither intuitive nor very informative. Because of the wide diversity of the various viral load profiles (Figure 3 of manuscript), the population based diagnostic plots have limited meaning for the assessment of the goodness of fit. In principle, the population prediction would be the same for a null-responder, a breakthrough patient, a patient having a relapse and a SVR patient. This implies that conditional estimates of the model parameters should be taken into account for model diagnostics based on population predictions to make sense. A plot of the population weighted residuals (WRES) *versus* PRED [Figure S6] shows a certain pattern which can be well explained by comparing the time course of the population predicted viral load with the individual viral load values. In order to assess the expected pattern of the DV *versus* PRED and WRES *versus* PRED plots of our model, mirror plots were created in which “observations” were simulated three times from the final model and these “observations” were subsequently re-fitted to create the PRED and WRES plots based on the parameters used in the simulation (Figures S5-
S6). The patterns of the PRED- and WRES-based diagnostics for the observed and simulated data were similar, implying that the observed pattern of these two population-based diagnostic plots matched with the expected pattern for our model (S8).

As population-based diagnostics were not very informative, goodness of fit was assessed based on diagnostic plots for the individual predictions (IPRED) [Figure S7], individual weighted residuals (IWRES) [Figure S8] and the absolute values of the individual weighted residuals (IWRESl) [Figure S9]. The ε-shrinkage was calculated to be 9%, implying that individual predictions can be used as a reliable diagnostic (S8). Mirror plots were also created for IPRED, IWRES and |IWRESl (Figures S7-S9). The patterns of the goodness of fit plots for IPRED, IWRES and |IWRESl for the observed and simulated data were similar, implying that no model misspecification was evident from the diagnostic (S8), and thus indicating that the individual viral load profiles are well described by the model. In addition, the goodness of fit plot of |IWRESl versus IPRED indicates that the residual error model was appropriate.

The η-shrinkage was calculated to be 39% for the basic reproduction number ($R_0$), 17% for the free virion clearance rate ($c$), 31% for the infected cell death rate ($\delta$) and 34% for $ED_{50,req}$. As anticipated, the relatively high shrinkage values are driven by the typical viral load profiles of the different patient categories (i.e., null-responders, breakthrough patients, relapsing patients and patients having an SVR). For instance, the shrinkage of $\delta$, describing the second phase of the viral load decay, was only 4% in breakthrough patients and 17% in patients having a relapse. These two patient categories generally have a relatively slow decay of the viral load so that the individual values of $\delta$ can be well estimated. SVR-patient viral load decline was generally characterized by a fast decay so that the second phase is not always visible, while null or partial responding
patients, had a relatively flat profile, and the $\delta$ estimate was more shrunken towards the population mean.

**Supplementary text note 5: performance of model-based SVR classification**

Statistical measures of the performance of the SVR classification by the HCV viral kinetic model were obtained by comparing the SVR classification (SVR or non-SVR) based on the model to the observed SVR classification in each individual patient present in the database of 2,100 CHC patients. Since by definition, the proposed model does not characterize SVR directly, but SVR is derived from crossing the model *cure* boundary, the performance of the model related to correctly classifying patients could be assessed by calculating the sensitivity and specificity based on individual predictions of HCV RNA including those obtained post-treatment (9,10) without confounding bias. A total of 941 patients were found to be True Positive (observed SVR and model-predicted SVR), and 1,119 CHC patients were found to be True Negative (observed non-SVR and model-predicted non-SVR) [Table S1]. A total of 33 patients were found to be False Negative (observed SVR but model-predicted non-SVR), and 7 patients were found to be False Positive (observed non-SVR but model-predicted SVR). Based on these numbers, the sensitivity and specificity was calculated to be 96.6% and 99.4%, respectively. Although the difference in the number of correctly and incorrectly classified individuals is quite convincing, it should be noted that the sensitivity and specificity are positively biased as the rows and columns of Table S1 are not fully independent. The positive predictive value (PPV) and negative predictive value (NPV) was calculated to be 99.3% and 97.1%, respectively. In calculating these two statistics, it is assumed that the prevalence in the population at large is similar.
**Figure S1.** Simulated long-term viral load profiles in 12 CHC patients receiving a 48-week treatment. Viral load profiles were simulated assuming $R_0 = 8$, $p = 6$ virions·cell$^{-1}$·day$^{-1}$, $c = 3$ day$^{-1}$, $\delta = 0.2$ day$^{-1}$, $r = 0.005$ day$^{-1}$ and an inhibition of the virion production of 80%. IIV was assumed to be 40% CV for $R_0$ and 20% CV for all other parameters. Simulated individual viral load data are either detectable (closed circles) or below the LLOQ of 50 IU/mL (closed triangles). Dotted horizontal lines show the LLOQ of the assay. Vertical lines indicate the end of treatment at 48 weeks.
Figure S2. Simulated HCV viral load (black line) and simulated number of infected hepatocytes (grey dashed line) with only one infected cell remained at the end of treatment. The simulation was performed with $R_0 = 8$, $p = 6$ virions·cell$^{-1}$·day$^{-1}$, $c = 3$ day$^{-1}$, $\delta = 0.2$ day$^{-1}$ and liver proliferation rate $r = 0.005$ day$^{-1}$. The dotted horizontal lines show the LLOQ of the assay of 50 IU/mL.
**Figure S3.** Simulated HCV viral load profiles during a 192-week antiviral therapy resulting in a continuous 50% inhibition of the virion production ($\varepsilon = 0.5$). Simulations were performed with $p = 6$ virions·cell$^{-1}$·day$^{-1}$, $c = 3$ day$^{-1}$, $\delta = 0.16$ day$^{-1}$ and $r = 0.01$ day$^{-1}$. The dotted horizontal line shows the LLOQ of the assay of 50 IU/mL. The basic reproductive number ($R_0$) was assumed to be 2.4, 2.2, 2.1, 2.0, 1.9 and 1.8, respectively resulting in a basic reproduction number in the presence of a 50% inhibition of the virion production ($R_T$) of 1.2, 1.1, 1.05, 1.0, 0.95 and 0.9 (see equation S1). Simulations confirmed that when $R_T < 1$, the infection will be cleared in the long run. But if $R_T > 1$, the infection will expand. When $R_T = 1$, the infection will not be cleared or expand but remain at some quasi-disease equilibrium.
Figure S4. Simulated liver regeneration after a donor remnant liver volume of 50%, 60%, 70%, 80% and 90% of the original total liver volume. Simulations were performed with the model estimated maximum liver proliferation rate ($r$) of 0.006 day$^{-1}$. 
Figure S5. Mirror plot of the observed versus population predictions (PRED) for the HCV viral kinetic model fitted to the actual data (upper left panel) and when all “observations” are simulated three times with the same model as is used to calculate the individual predictions (upper right panel and lower panels). The predicted values are based on the estimated parameter values. The solid black line is the line of identity which should go through the middle of the data. Simulations were undertaken with an LLOQ of 50 IU/mL explaining the presence of more lower “observed” values in the simulations.
Figure S6. Mirror plot of the weighted residuals (WRES) versus population predictions (PRED) for the HCV viral kinetic model fitted to the actual data (upper left panel) and when all “observations” are simulated three times with the same model as is used to calculate the WRES (upper right panel and lower panels). The solid black line is the zero line.
Figure S7. Mirror plot of the observed versus individual predictions (IPRED) for the HCV viral kinetic model fitted to the actual data (upper left panel) and when all “observations” are simulated three times with the same model as is used to calculate the individual predictions (upper right panel and lower panels). The predicted values are based on the estimated parameter values. The grey line represents a smooth through the data. The solid black line is the line of identity which should go through the middle of the data. Simulations were undertaken with an LLOQ of 50 IU/mL explaining the presence of more lower “observed” and IPRED values in the simulations.
Figure S8. Mirror plot of the individual weighted residuals (IWRES) versus individual predictions (IPRED) for the HCV viral kinetic model fitted to the actual data (upper left panel) and when all “observations” are simulated three times with the same model as is used to calculate the IWRES (upper right panel and lower panels). The grey line represents a smooth through the data. The solid black line is the zero line around which the values of IWRES should be randomly and densely scattered. Simulations were undertaken with an LLOQ of 50 IU/mL explaining the presence of more lower IPRED values in the simulations. Some higher IWRES values are present for small IPRED values based on the actual data. However, these data points present only a minor fraction of the overall data.
Figure S9. Mirror plot of the absolute values of the individual weighted residuals (|IWRES|) versus individual predictions for the HCV viral kinetic model fitted to the actual data (upper left panel) and when all “observations” are simulated three times with the same model as is used to calculate the |IWRES| (upper right panel and lower panels). Simulations were undertaken with an LLOQ of 50 IU/mL explaining the presence of more lower IPRED values in the simulations. Some higher |IWRES| values are present for small IPRED values based on the actual data. However, these data points present only a minor fraction of the overall data.
Table S1. Calculation of the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the model-based classification of CHC patients into SVR or non-SVR.

<table>
<thead>
<tr>
<th>Fitted SVR</th>
<th>Observed SVR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SVR = 1</td>
<td>SVR = 0</td>
</tr>
<tr>
<td>SVR = 1</td>
<td>True Positive</td>
<td>False Positive</td>
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<tr>
<td></td>
<td>941</td>
<td>7</td>
</tr>
<tr>
<td>SVR = 0</td>
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<td>True Negative</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>1119</td>
</tr>
<tr>
<td>Total</td>
<td>974</td>
<td>1,126</td>
</tr>
<tr>
<td></td>
<td>Sensitivity(^1) = 96.6%</td>
<td>Specificity(^2) = 99.4%</td>
</tr>
</tbody>
</table>

\(^1\)Sensitivity is calculated as 941 divided by 974 and expressed as %.
\(^2\)Specificity is calculated as 1,119 divided by 1,126 and expressed as %.
\(^3\)Positive predicted value (PPV) is calculated as 941 divided by 948 and expressed as %.
\(^4\)Negative predictive value (NPV) is calculated as 1,119 divided by 1,152 and expressed as %.
References for supporting online material


