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Sustained virological response with intravenous silibinin: individualized IFN-free therapy via real-time modeling of HCV kinetics

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Abstract

Background & Aims—Intravenous silibinin (SIL) is a potent antiviral agent against hepatitis C virus (HCV) genotype-1. In this proof of concept case-study we tested: (i) whether interferon-alfa (IFN)-free treatment with SIL plus ribavirin (RBV) can achieve sustained virological response (SVR), (ii) whether SIL is safe and feasible for prolonged duration of treatment, and (iii) whether mathematical modeling of early on-treatment HCV kinetics can guide duration of therapy to achieve SVR.

Methods—A 44 year-old female HCV-(genotype-1)-infected patient who developed severe psychiatric adverse events to a previous course of pegIFN+RBV, initiated combination treatment with 1200 mg/day of SIL, 1200 mg/day of RBV and 6000 u/day vitamin D. Blood samples were collected frequently till week 4, thereafter every 1 to 12 weeks until the end of therapy. The standard-biphasic-mathematical model was used to predict the duration of therapy to achieve SVR.

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Authors' contribution:
H.D., M.D., R.T.P and Y.L. designed the research. S.S., I.G., G.W., Y.J.A., T.T., E.G., and Y.L. provided the clinical data. H.D., S.S., S.J.C., and Y.L. analyzed and modeled the data. H.D., S.S., S.J.C., M.D., and Y.L. wrote the paper.

Results—Based on modeling the observed viral kinetics during the first 3 weeks of treatment, SVR was predicted to be achieved within 34 weeks of therapy. Provided with this information, the patient agreed to complete 34 weeks of treatment. IFN-free treatment with SIL+RBV was feasible, safe, and achieved SVR (week-33).

Conclusions—We report, for the first time, the use of real-time mathematical modeling of HCV kinetics to individualize duration of IFN-free therapy and to empower a patient to participate in shared decision making regarding length of treatment. SIL-based individualized therapy provides a treatment option for patients who do not respond to or cannot receive other HCV agents and should be further validated.

Keywords

hepatitis C; silibinin; mathematical modeling; viral kinetics; sustained virological response; interferon-free treatment; individualized therapy

Introduction

The recent approval of direct-acting antiviral agents (DAAs), the HCV NS3/4A protease inhibitors (boceprevir, telaprevir, and simeprevir) and the HCV nucleotide polymerase inhibitor sofosbuvir represents an important milestone in achieving higher sustained virological response (SVR) rates [1]. IFN-free DAA therapeutic regimens for HCV genotype 1 are expected in the next few years but success will not be measured only by SVR rates but also by the availability of effective treatment for all individuals infected with HCV [2].

Legalon SIL (SIL) is a chemically hydrophilized version of silibinin that has high antiviral efficacy against HCV in patients with compensated liver disease during SIL alone or in combination with pegIFN [3, 4], and is well tolerated in the peri-liver transplantation (LT) period [5]. While SIL has been extensively studied and even prevented HCV infection of liver grafts after LT (reviewed in [6]), IFN-free SIL-based therapy has not been administered for prolonged time periods (> 4 weeks)in order to treat chronic HCV.

Mathematical modeling of viral kinetics has provided valuable insights for the understanding of HCV-host-drug dynamics and pathogenesis. In particular, it has been proposed that modeling can ultimately determine the duration of treatment needed for SVR [7-9]. In the current case study we sought to provide a proof-of-concept for the safety and feasibility of IFN-free treatment with SIL+RBV and to assess the utility of mathematical modeling of early on treatment viral kinetics to individualize and optimize the duration of therapy needed for cure.

Patient and Methods

Patient & therapy

A 44 year-old female HCV-(genotype 1)-infected patient who developed severe psychiatric adverse events to a previous course of pegylated interferon-alpha-2a plus ribavirin, agreed to initiate a combination treatment with 1200 mg/day of SIL (corresponding to 20 mg/kg/day)

and 1200 mg/day of ribavirin. Based on a growing body of in vitro [10] and in vivo [11, 12] studies about the antiviral activity of vitamin D and its role in HCV treatment outcomes, 6000 u/day of vitamin D was given to the patient as a supplemental treatment. Her fibrosis stage was F1 based on Fibrotest™. The pre-treatment hemoglobin level was 12.8 g/dL. The treatment was approved by the Institutional Review Board at the Share'e Zedek Medical Center and the patient provided verbal consent.

HCV RNA measurements

Blood samples were collected frequently at days 0, 2, 4, 7, 11, 15, 21 and 23, thereafter weekly until week 8 and then every 2 to 12 weeks until the end of therapy (Fig. 1). After treatment cessation, blood was collected at weeks 4, 8, 14 and 33. HCV RNA was measured using the Abbot RealTime assay with lower level of quantitation and detection of 12 IU/ml.

Mathematical modeling

To explain the biphasic HCV viral decline observed in our patient under SIL+RBV therapy (Fig. 1), the standard biphasic model, Neumann et al [13], was used:

$$\begin{aligned} \frac{dI}{dt} &= (1-\eta)\,\beta T_0 V - \delta I \\ \frac{dV}{dt} &= (1-\varepsilon(t))\,pI - cV, \end{aligned} \quad \text{(Eq. 1)}$$

where I represents HCV-infected cells and V, free HCV in blood. HCV, V, infects target cells, T_0, with constant rate β, generating infected cells, I, which produce new virions at rate p per infected cell. Infected cells are lost at a rate δ per infected cell and virions are assumed to be cleared at rate c per virion. SIL+RBV effectiveness in blocking infection is modeled by a factor (1-η), where η is defined as the drug effectiveness in blocking infection. We assume that RBV does not affect viral production [14], but for SIL we used either a constant effectiveness (CE), i.e., $\varepsilon(t)$=constant as in [13], or a time-varying effectiveness (VE), $\varepsilon(t)$, as in [15], where$\varepsilon(t)=\varepsilon\ (1\text{-}\exp^{-\kappa t}\ \text{max}\ )$, and the change in SIL effectiveness from 0 to the final effectiveness, ε_{max}, is described by a rate constant κ.

Parameter estimation

We assume the target cell (i.e., hepatocytes) level per ml was constant, i.e., 1×10^7cells/ml (described in [14]), and the initial infected cell level is represented by the steady state pre-treatment level of $I_0=\beta V_0 T_0/\delta$. Due to lack of frequent sampling, especially during the first 2 days after initiation of therapy, the pharmacological delay of SIL, t_0, and the effectiveness of SIL in blocking HCV entry, η, were fixed to 0.66 h, and 0.6, respectively, as determined in our previous SIL modeling study [4].We assume that the addition of RBV does not significantly increase the effect of SIL in blocking infection, i.e., η=0.6. Parameter β was set to 2×10^{-7} ml/virion/day to allow a low fraction of HCV-infected hepatocytes (~8%), within the range estimated in [16]. The remaining parameters were estimated by fitting the model with the observed data using Berkeley Madonna (V.8.3).

Prediction of duration of therapy to achieve SVR

The time to cure, or SVR, was defined as the time to reach less than one hepatitis C virion and one infected cell in the extracellular fluid volume (~13.5L to ~15L)[7, 8, 13]. To be

highly conservative, we chose a threshold of 2×10^{-5} IU/ml. Note that the prediction of SVR is based on the assumption that the slower viral decline rate, (or 2nd phase), continues at the same decline rate throughout SIL treatment.

Case report

HCV rapidly declined in a biphasic manner from 45,000 IU/ml to below assay detection (12 IU/ml) by day 23 and remained undetectable thereafter (Fig. 1). The only clinical adverse event was a mild feeling of warmth during SIL infusion that correlated with the rate of the infusion. Laboratory adverse events were limited to mild reversible eosinophilia (max value ~1200 eosinophils), which persisted during the first 5 months of therapy and a decline in hemoglobin level to 10.8 g/dL that led to RBV dose reduction to 1000 mg/kg at day 38 post initiation of therapy. Three days before RBV reduction SIL dose was increased to 1400 mg/day, i.e., 23 mg/kg/day until the end of therapy.

Fitting the constant effectiveness (CE) model to the data led to an excellent goodness of fit (Fig. 1A, gray solid line) but with a surprisingly small HCV clearance rate of c=1.7/day (Table 1), which was substantially lower than what has been typically found with IFN-based therapy (6/day) [13]. Although the CE model attributes this slow decline to a low rate of viral clearance from blood, this interpretation is dubious as the endogenous rate of viral clearance is a constant physiological quantity and, consequently, *c* should not depend on the antiviral strategy. To address this concern, we set c=6/day as in [4] , but used the VE model to explore the possibility of a gradual increase of SIL antiviral effectiveness over time. The VE model yielded an excellent fit of the data (Fig. 1A, black solid line), with maximum SIL effectiveness, ε_{max}=0.998 and change rate in treatment effectiveness κ=1.4/day. The loss rate of infected cells was estimated δ=0.102/day (Table 1).

Since the VE model provided a better fit than the CE model, assuming that c=6/day, the time to cure was predicted based on the VE model. The time of viral and infected cell eradication from total plasma and extracellular fluid was predicted to be achieved between 25 and 34 weeks, respectively (Fig. 1B, when black solid and dashed lines cross the horizontal cure boundary line). While the prediction of the time to the last virion in circulation was somewhat robust, the time to eradication of the last infected cell was more speculative due to lack of experimental data on the infected cell level. For a theoretical exercise, if the baseline fraction of infected cell level was extremely small ~0.01% (i.e., infection rate constant of $\beta=2.4\times10^{-10}$ ml/virion/day), which is unlikely but still possible in some cases, the time to infected cell eradication would be ~25 weeks, i.e., similar to the eradication of the virus (not shown). Alternatively, if the fraction of infected cells was about 8% (see Methods), the time to infected cell eradication would be 34 weeks. As such, the modeling suggested that while a minimum duration of 25 weeks of therapy might be sufficient to clear the virus from the blood, an additional 9 weeks of therapy may be needed to eradicate the last productive HCV-infected cell.

Patient shared decision making & treatment outcome

Provided with the modeling predictions, the patient chose to complete 34 weeks of treatment. Overall, SIL treatment was well tolerated with 100% adherence and the patient

did not miss a single day of work. Post treatment, HCV remained undetectable at weeks 4, 8, 14 and 33 (SVR 33).

Discussion

This case study provides three main proof-of-concept findings: (i) SIL+RBV is safe and feasible for long (i.e., 34 weeks) duration of therapy, (ii) IFN-free treatment with SIL+RBV can alone achieve SVR and (iii) mathematical modeling, early on treatment, can help individualize and optimize duration of therapy and empower patients to participate in shared decision making.

The addition of DAAs to pegylated-interferon (IFN) and ribavirin (RBV) constitutes a new stage in HCV therapy [1] and preliminary data from a number of IFN free DAA combinations are quite promising. However, there are a number of patient groups who could potentially benefit from SIL-based therapy. The SVR rates of even the most effective DAA regimens fall short of 100% for genotype 1 patients and compensated cirrhotic and nonresponder patients could be considered for novel treatment approaches such as SIL plus RBV. In addition to having antiviral activity against genotypes 1 and 4 [3, 15], SIL appears to suppress viral load in patients infected with HCV genotype 3 [5, 17, 18] which suggests that SIL-based therapy could potentially improve treatment outcomes in difficult-to-treat patients infected with HCV genotype 3 [19]. In contrast, SIL did not prevent graft reinfection in a patient with HCV genotype 2 [20], calling into question whether it has activity against genotype 2 [21]. SIL was also shown to inhibit HCV (genotype 1b) and, to a lesser extent, HIV-1 in a patient coinfected with HCV and HIV-1 [22]. Moreover, SIL was recently shown to be safe and to have potent antiviral activity in patients with decompensated cirrhosis [5, 15] and in liver transplant recipients [18, 23, 24]. In these special cases, SIL-based therapy could provide an important alternative therapeutic approach, which would outweigh the inconvenience of daily IV SIL administration.

Although the exact mechanism of action of SIL against HCV is controversial [25], SIL appears to induce two classes of viral RNA decay profiles, suggesting the possibility that both direct antiviral (probably by RNA dependent RNA polymerase inhibition and later steps in virion release [21]) and blocking infection mechanisms contribute to the anti-HCV effects of SIL [26]. This may explain, in part, the surprising lack of resistance (e.g., viral breakthrough) to SIL monotherapy, with durations of 7 to 21 days [3-5], in chronic HCV-infected patients. Recent results [27] with SIL treatment in HCV-infected uPA-SCID chimeric mice with humanized livers indicate a 2nd phase decline in serum HCV in the absence of an adaptive immune response that may rule out the importance of any adaptive immunomodulatory effect of SIL [28].

For over 20 years, intravenous SIL has provided a well-tolerated and safe treatment for Amanita phalloides-induced acute liver failure [29]. Not surprisingly, in the setting of chronic HCV infection, SIL was associated with minimal side effects; only heat sensation and mild sweating during the first infusion and a transient increase in bilirubin levels during the first 2 weeks of infusions [21]. A growing experience with SIL therapy shows that motivated patients with adequate support can successfully complete a course of daily

intravenous infusions without significant disruption of their daily activities. In previous studies, short courses of intravenous SIL were found to be feasible and to have high rates of adherence [21]. In the current case report, we for the first time show that a longer course of SIL (238 consecutive days) was feasible and safe with 100% adherence and the patient did not miss a single day of work during therapy.

While the use of mathematical modeling and early viral kinetics were previously tested during therapy with pegIFN±RBV±histamine in order to increase SVR rates [30], our multidisciplinary approach constitutes a milestone in the use of mathematical modeling to individualize and optimize duration of IFN-free therapy with SIL+RBV. Mathematical modeling of HCV infection and treatment has played a valuable role in understanding HCV dynamics, the mechanism of action and effectiveness of anti-HCV drugs, HCV pathogenesis and the duration of therapy needed for SVR [4, 8, 13, 31, 32]. The recently approved oral DAAs are costly [33], and it is expected that future all-oral DAA regimens for HCV genotype-1 might be in the range of $100,000 to $150,000 per treatment course. The total cost of a course of SIL, which might be considered for patients without other treatment options, will depend on the duration of therapy and how SIL is priced in different countries. The cost will be much reduced in patients with a faster 2nd phase slope decline. For example, a patient with a 2-fold higher δ than the current case (i.e.δ=0.2/day), would need a projected 100 days of SIL therapy to eradicate the virus and ~40 more days to eradicate the last infected cell. Another option for future study that could result in cost reduction would be a short course of SIL with oral DAAs in nonresponders to DAA therapy. The high cost of current and expected treatment for hepatitis C (especially for genotype 1 and 4) highlights the importance of ongoing efforts to further utilize modeling viral kinetics for individualized therapy that may prove more cost effective [9].

In conclusion, SIL-based individualized therapy, via mathematical modeling of early HCV kinetics, might be considered a treatment option for patients who do not respond to or cannot be treated with DAA regimens. Additional studies with recently FDA-approved protease inhibitors and other emerging DAA compounds, e.g., sofosbuvir, are required to formally demonstrate the efficacy of SIL in conjunction with new antivirals.

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Abbreviations

SIL	Legalon Silibinin
HCV	hepatitis C virus
IFN	interferon-alfa
RBV	ribavirin

SVR	sustained virological response
DAAs	direct-acting antiviral agents
LT	liver transplantation
CE	constant effectiveness
VE	time-varying effectiveness

References

1. Dugum M, O'Shea R. Hepatitis C virus: Here comes all-oral treatment. Cleveland Clinic journal of medicine. 2014; 81:159–172. [PubMed: 24591471]
2. Aronsohn A, Muir AJ, Swan T, Jensen D. Is the HCV pipeline heading in the right direction? Gastroenterology. 2013; 144:482–485. [PubMed: 23352458]
3. Ferenci P, Scherzer TM, Kerschner H, Rutter K, Beinhardt S, Hofer H, et al. Silibinin is a potent antiviral agent in patients with chronic hepatitis C not responding to pegylated interferon/ribavirin therapy. Gastroenterology. 2008; 135:1561–1567. [PubMed: 18771667]
4. Guedj J, Dahari H, Pohl RT, Ferenci P, Perelson AS. Understanding silibinin's modes of action against HCV using viral kinetic modeling. Journal of hepatology. 2012; 56:1019–1024. [PubMed: 22245888]
5. Marino Z, Crespo G, D'Amato M, Brambilla N, Giacovelli G, Rovati L, et al. Intravenous silibinin monotherapy shows significant antiviral activity in HCV-infected patients in the peri-transplantation period. Journal of hepatology. 2013; 58:415–420. [PubMed: 23063567]
6. Polyak SJ, Oberlies NH, Pecheur EI, Dahari H, Ferenci P, Pawlotsky JM. Silymarin for HCV infection. Antivir Ther. 2013; 18:141–147. [PubMed: 23011959]
7. Snoeck E, Chanu P, Lavielle M, Jacqmin P, Jonsson EN, Jorga K, et al. A comprehensive hepatitis C viral kinetic model explaining cure. Clin Pharmacol Ther. 2010; 87:706–713. [PubMed: 20463660]
8. Dixit NM, Layden-Almer JE, Layden TJ, Perelson AS. Modelling how ribavirin improves interferon response rates in hepatitis C virus infection. Nature. 2004; 432:922–924. [PubMed: 15602565]
9. Dahari H, Cotler SJ. Individualized treatment for patients with low HCV load (genotype 1): A viral kinetic approach. Hepatology. 2014 in press.
10. Gal-Tanamy M, Bachmetov L, Ravid A, Koren R, Erman A, Tur-Kaspa R, et al. Vitamin D: an innate antiviral agent suppressing hepatitis C virus in human hepatocytes. Hepatology. 2011; 54:1570–1579. [PubMed: 21793032]
11. Gutierrez JA, Parikh N, Branch AD. Classical and emerging roles of vitamin D in hepatitis C virus infection. Seminars in liver disease. 2011; 31:387–398. [PubMed: 22189978]
12. Abu-Mouch S, Fireman Z, Jarchovsky J, Zeina AR, Assy N. Vitamin D supplementation improves sustained virologic response in chronic hepatitis C (genotype 1)-naive patients. World journal of gastroenterology : WJG. 2011; 17:5184–5190. [PubMed: 22215943]
13. Neumann AU, Lam NP, Dahari H, Gretch DR, Wiley TE, Layden TJ, et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. Science. 1998; 282:103–107. [PubMed: 9756471]
14. Dahari, H.; Shudo, E.; Ribeiro, RM.; Perelson, AS. Mathematical modeling of HCV RNA kinetics.. In: Tang, H., editor. Hepatitis C Protocols. 2nd ed.. Humana Press; NJ: 2009.
15. Canini L, DebRoy S, Marino Z, Conway JM, Crespo G, Navasa M, et al. Severity of liver disease affects HCV kinetics in patients treated with intravenous silibinin monotherapy. Antiviral Therapy. 2014
16. Liang Y, Shilagard T, Xiao SY, Snyder N, Lau D, Cicalese L, et al. Visualizing hepatitis C virus infections in human liver by two-photon microscopy. Gastroenterology. 2009; 137:1448–1458. [PubMed: 19632233]

17. Rutter K, Scherzer TM, Beinhardt S, Kerschner H, Stattermayer AF, Hofer H, et al. Intravenous silibinin as 'rescue treatment' for on-treatment non-responders to pegylated interferon/ribavirin combination therapy. Antivir Ther. 2011; 16:1327–1333. [PubMed: 22155914]
18. Neumann UP, Biermer M, Eurich D, Neuhaus P, Berg T. Successful prevention of hepatitis C virus (HCV) liver graft reinfection by silibinin mono-therapy. Journal of hepatology. 2010; 52:951–952. [PubMed: 20413176]
19. Goossens N, Negro F. Is genotype 3 of the hepatitis C virus the new villain? Hepatology. 2014; 59:2403–2412. [PubMed: 24155107]
20. Aghemo A, Bhoori S, De Nicola S, Mazzaferro V, Colombo M. Failure of Intravenous Silibinin Monotherapy to Prevent Hepatitis C Genotype 2A Liver Graft Reinfection. Hepatitis monthly. 2012; 12:411–414. [PubMed: 22879832]
21. Polyak SJ, Ferenci P, Pawlotsky JM. Hepatoprotective and antiviral functions of silymarin components in hepatitis C virus infection. Hepatology. 2013; 57:1262–1271. [PubMed: 23213025]
22. Payer BA, Reiberger T, Rutter K, Beinhardt S, Staettermayer AF, Peck-Radosavljevic M, et al. Successful HCV eradication and inhibition of HIV replication by intravenous silibinin in an HIV-HCV coinfected patient. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2010; 49:131–133. [PubMed: 20709593]
23. Beinhardt S, Rasoul-Rockenschaub S, Scherzer TM, Ferenci P. Silibinin monotherapy prevents graft infection after orthotopic liver transplantation in a patient with chronic hepatitis C. Journal of hepatology. 2011; 54:591–592. author reply 592-593. [PubMed: 21106270]
24. Eurich D, Bahra M, Berg T, Boas-Knoop S, Biermer M, Neuhaus R, et al. Treatment of hepatitis C-virus-reinfection after liver transplant with silibinin in nonresponders to pegylated interferon-based therapy. Experimental and clinical transplantation : official journal of the Middle East Society for Organ Transplantation. 2011; 9:1–6. [PubMed: 21605016]
25. Dahari H, Guedj J, Perelson AS. Silibinin mode of action against hepatitis C virus: a controversy yet to be resolved. Hepatology. 2011; 54:749. [PubMed: 21433039]
26. Blaising J, Levy PL, Gondeau C, Phelip C, Varbanov M, Teissier E, et al. Silibinin inhibits hepatitis C virus entry into hepatocytes by hindering clathrin-dependent trafficking. Cellular microbiology. 2013; 15:1866–1882. [PubMed: 23701235]
27. DebRoy S, Hiraga N, Imamura M, Canini L, Pohl RT, Persiani S, et al. HCV kinetics in uPA-SCID chimeric mice with humanized livers during intravenous silibinin monotherapy. Hepatology. 2014; 60(Suppl) (accepted).
28. Morishima C, Shuhart MC, Wang CC, Paschal DM, Apodaca MC, Liu Y, et al. Silymarin inhibits in vitro T-cell proliferation and cytokine production in hepatitis C virus infection. Gastroenterology. 2010; 138:671–681. 681, e671–672. [PubMed: 19782083]
29. Klein AS, Hart J, Brems JJ, Goldstein L, Lewin K, Busuttil RW. Amanita poisoning: treatment and the role of liver transplantation. The American journal of medicine. 1989; 86:187–193. [PubMed: 2643869]
30. Zeuzem S, Pawlotsky JM, Lukasiewicz E, von Wagner M, Goulis I, Lurie Y, et al. International, multicenter, randomized, controlled study comparing dynamically individualized versus standard treatment in patients with chronic hepatitis C. Journal of hepatology. 2005; 43:250–257. [PubMed: 16082736]
31. Guedj J, Dahari H, Rong L, Sansone ND, Nettles RE, Cotler SJ, et al. Modeling shows that the NS5A inhibitor daclatasvir has two modes of action and yields a shorter estimate of the hepatitis C virus half-life. Proc Natl Acad Sci U S A. 2013; 110(10):3991–3996. [PubMed: 23431163]
32. Guedj J, Perelson AS. Second-phase hepatitis C virus RNA decline during telaprevir-based therapy increases with drug effectiveness: implications for treatment duration. Hepatology. 2011; 53:1801–1808. [PubMed: 21384401]
33. Hill A, Cooke G. Medicine. Hepatitis C can be cured globally, but at what cost? Science. 2014; 345:141–142. [PubMed: 25013048]

Key Points

- IFN-free silibinin (SIL)-based therapy has not been administered for prolonged time periods (>4 weeks) in order to treat chronic HCV.
- We report, for the first time, the use of real-time mathematical modeling of HCV kinetics to individualize duration of IFN-free therapy with SIL plus ribavirin and to empower a patient to participate in shared decision making regarding length of treatment.
- Thirty four weeks of IFN-free treatment with SIL+ribavirin was feasible, safe, and achieved sustained virological response.
- SIL-based individualized therapy may provide a treatment option for patients who do not respond to or cannot receive other HCV agents

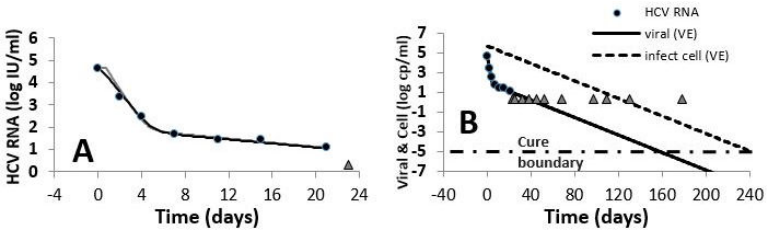

Fig. 1.

Model fits with empirical kinetic data and predicted time to cure. (A) Best curve fits of CE (gray line) and VE (black line) models with observed data; (B) Based on the VE model, which yields a better fit than the CE model, virus is predicted to be eradicated from the circulation by 175 days (25 weeks) and infected cells by 238 days (34 weeks).Not detectable HCV RNA , i.e., <12 IU/ml (gray filled triangles), measured during therapy, were arbitrarily set to 0.3 log IU/ml. Estimated viral and host parameters are shown in Table 1.

Table 1

Parameter estimation and prediction duration of therapy

Model	t_0 [h]	c [1/day]	ε or ε_{max}	κ [1/day]	δ [1/day]	Time for <1 virus [wk]	Time for <1 infected cell [wk]	RMS
CE	0.6*	1.8	0.998	----	0.107	21	33	0.14
VE	0.0*	6.0*	O.998	1.37	0.098	25	34	0.09

CE, constant effectiveness model; VE, varying effectiveness model

*fixed parameters; t_0, pharmacological delay of SIL; c, HCV clearance rate from blood; ε, SIL effectiveness (CE model) in blocking HCV production/release; ε_{max}, maximum effectiveness (VE model) in blocking HCV production/release; κ, SIL effectiveness increase rate (VE model); δ, loss rate of infected cells; RMS, root mean square of the differences between observed data points and best fit curve (the lower the better).