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Treatment of hepatitis C with an interferon-based lead-in phase: A perspective from mathematical modeling

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Abstract

Background—The standard of care for hepatitis C virus (HCV) genotype 1 is a protease inhibitor (telaprevir or boceprevir) combined with pegylated interferon and ribavirin (P/R). A lead-in phase of P/R therapy before addition of the protease inhibitor has been used, with the aim of improving response rates by reducing the development of protease inhibitor resistance. However, whether such a strategy can bring benefit to patients is unclear.

Methods—A viral dynamic model was used to compare in silico HCV dynamics in patients treated with a period of P/R lead-in therapy followed by the addition of a protease inhibitor versus immediate triple therapy without lead-in.

Results—The model predicts that both regimens result in a similar end of treatment viral load change (viral decline or breakthrough). Thus, the current lead-in strategy may not decrease the rate of viral breakthrough/relapse or increase the rate of sustained virologic response. This agrees with available data from clinical trials of several HCV protease inhibitors, such as telaprevir, boceprevir, and faldaprevir.

Conclusions—These results suggest that current P/R lead-in strategies may not improve treatment outcomes. However, virus kinetics during a period of P/R therapy, combined with other factors such as the IL28B polymorphism and baseline viral load, can identify interferon-sensitive patients and help develop response-guided therapies.

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Disclosure statement
All authors declare no conflict of interest.

Additional file
An additional file “Supplementary material” is attached.

Introduction

Treating hepatitis C virus (HCV) infection with a combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) achieves sustained virologic response (SVR) in <50% of patients infected with genotype 1 virus [1, 2]. Two protease inhibitors, telaprevir and boceprevir, are now being used to treat HCV genotype 1 infection when used in combination with PEG-IFN and RBV (P/R). The addition of either of them to P/R has significantly increased the rate of SVR, but relapse at the end of treatment and on-treatment viral breakthrough are still concerns [3–9].

A lead-in phase of P/R has been used in various clinical trials involving protease inhibitors and in the approved therapy using boceprevir with the aim of decreasing the probability of relapse or viral breakthrough caused by the development of protease inhibitor resistance [5–8, 10–13]. In the open-label, randomized SPRINT-1 trial [5, 13], 107 HCV-infected treatment-naive patients were treated with a triple combination of boceprevir, PEG-IFN-α-2b, and RBV for 28 wks. About 30% relapsed after the end of therapy and 7% had viral breakthrough. Of 103 patients who received a 4-wk lead-in of P/R followed by addition of boceprevir for another 24 wks, 24% relapsed and 4% had viral breakthrough but these differences were not significant (p=0.4 for relapse and p=0.387 for viral breakthrough). When the duration of treatment was 48 wks, the lead-in group (4-wk P/R followed by 44 wks of triple therapy, n=103) had a 3% relapse rate and a 5% viral breakthrough rate. While these percentages increased to 7% and 12% in the no-lead-in group (n=103) [5], the differences were again not significant (p=0.204 for relapse and p=0.076 for viral breakthrough). The effect of the lead-in phase on the rate of SVR was also examined [5]. Patients receiving 28 wks of triple therapy had an SVR rate of 54%, similar to the 56% SVR rate for patients with the lead-in phase (p=0.759). In patients who received 48-wk therapy, the lead-in arm had a 75% SVR rate, higher than the 67% rate for the no-lead-in arm (p=0.22). While these data suggested that a lead-in phase might have some benefit to patients, they should be interpreted with caution because the sample size was relatively small and all the differences were not statistically significant. In fact, the number of studies on lead-in strategies is limited and the situation is further complicated by the fact that in these studies different lead-in durations were used and different drugs were added after the lead-in [5, 6, 10, 11] (available data from clinical trials with a lead-in phase are summarized in Table 1). Thus, it remains unclear whether a lead-in phase can improve treatment outcomes in hepatitis C patients [14].

Here we use a mathematical model to compare viral dynamics in in silico patients treated with and without a lead-in phase, and compare model predictions with available data of treatment responses. Parameters identified by analysis of patients treated with telaprevir [15] were used in the in silico simulations but the model and predictions can be applied to other protease inhibitors.

Methods

We use the following model to study the viral load change in patients treated with and without a lead-in phase of P/R. The model was used previously to analyze drug resistance

data from HCV patients treated with telaprevir alone or in combination with PEG-IFN-α-2a [15].

$$\begin{aligned} dT/dt &= s+\rho_T T(1-\tfrac{T+I_s+I_r+N}{T_{\max}})-dT-\beta V_s T-\beta V_r T \\ dI_s/dt &= \beta V_s T-\delta_s I_s \\ dI_r/dt &= \beta V_r T-\delta_r I_r \\ dV_s/dt &= (1-\mu)(1-\varepsilon_s)p_s I_s-cV_s \\ dV_r/dt &= \mu(1-\varepsilon_s)p_s I_s+(1-\varepsilon_r)p_r I_r-cV_r \end{aligned} \quad (1)$$

The model contains five variables: target cells (T), virions (V_s and V_r, the subscripts s and r represent drug sensitive and resistant, respectively), and cells infected by drug sensitive and drug resistant virions (I_s and I_r, respectively). Target cells are generated by differentiation from precursors at rate s, die at rate d, and proliferate with maximum rate ρ_T. T_{max} is the hepatocyte carrying capacity of the liver. N is the number of hepatocytes that are not target of HCV infection, possibly due to being in an IFN-induced antiviral state [16]. Virions infect cells at rate β. I_s and I_r are lost at rates δ_s and δ_r, and produce virions at rates p_s and p_r, respectively. I_s has a probability μ to generate drug resistant virions. The efficacies of treatment in reducing viral production are ε_s and ε_r. Virions are cleared at rate c.

With a lead-in phase of duration t_L, the drug efficacies are

$$\varepsilon_s = \begin{cases} \varepsilon_{lead}, & \text{if} \quad t<t_L \\ \varepsilon^s_{total}=1-(1-\varepsilon_{lead})(1-\varepsilon^s_{DAA}), & \text{if} \quad t \geq t_L \end{cases}$$
$$\varepsilon_r = \begin{cases} \varepsilon_{lead}, & \text{if} \quad t<t_L \\ \varepsilon^r_{total}=1-(1-\varepsilon_{lead})(1-\varepsilon^r_{DAA}), & \text{if} \quad t \geq t_L \end{cases} \quad (2)$$

where ε_{lead} is the effectiveness of lead-in therapy in reducing viral production. ε^s_{DAA} and ε^r_{DAA} are the efficacies of the added DAA in reducing production of DAA-sensitive and resistant virus, respectively. Thus, $1-(1-\varepsilon_{lead})(1-\varepsilon^s_{DAA})$ and $1-(1-\varepsilon_{lead})(1-\varepsilon^r_{DAA})$ are the overall efficacies of combination therapy against the two strains. If DAA is given with P/R simultaneously since the beginning of therapy, then $t_L = 0$, and $\varepsilon_s=\varepsilon^s_{total}$ and $\varepsilon_r=\varepsilon^r_{total}$.

A faster second-phase viral decline (corresponding to a larger estimate of the infected cell death rate [17]) was observed in patients receiving telaprevir than in those receiving IFN/PEG-IFN with/without RBV. For example, the estimate of the infected cell death rate in patients treated with telaprevir and PEG-IFN-α-2a (0.44 day^{-1} [15] and 0.55 day^{-1} [18]) is 5 to 10 times higher than that estimated in patients treated with PEG-IFN-α-2a (0.06 day^{-1} [18]) or IFN-α (0.14 day^{-1} [17]). The nature of this enhanced second phase decline is not fully established but it could involve cure of infected cells rather than loss by death [18–20]. We also took this potential difference in δ values into account in our comparison. We assumed that the death rate of cells that are infected with wild-type virus is δ_{lead} during the lead-in phase and increases to δ_{DAA} when a DAA is added, i.e.,

$$\delta_s = \begin{cases} \delta_{lead}, & \text{if} \quad t < t_L \\ \delta_{DAA}, & \text{if} \quad t \geq t_L \end{cases} \quad (3)$$

The death rate of cells that are infected with DAA-resistant virus is not affected by the addition of the DAA, i.e., $\delta_r = \delta_{lead}$. The steady states of model (1) before therapy were used as the initial conditions of the simulation under therapy.

In model (Eq. 1), we assumed therapy with P/R only reduces viral production. However, how RBV improves IFN response rates in HCV infection is unclear. In the Supplementary Material, we included a model (Eq. S1) assuming that RBV decreases HCV infectivity, as proposed by Dixit et al. [21]. We also incorporated the pharmacokinetic and pharmacodynamic parameters (Supplementary Eqs. S3 and S4) of weekly administered PEG-IFN-α [22] to evaluate the influence of time-varying drug efficacy on viral kinetics in patients treated with and without a lead-in phase.

Results

We used the model (Eq. 1) with Eqs. (2) and (3) to compare the predicted viral kinetics in in silico patients treated with and without 4 wks of P/R lead-in therapy followed by triple therapy. We also compared the predicted responses for three cases: (i) the patient is assumed to be very responsive to P/R (Fig. 1A); (ii) the patient is a partial responder (Fig. 1B); and (iii) the patient is a poor or null responder (Fig. 1C). We calculated the effectiveness of PEG-IFN using $\varepsilon_{lead} = D_{peg}/(D_{peg} + ED_{50})$, where D_{peg} is the weekly subcutaneous dose of PEG-IFN, and ED_{50} is the estimated weekly dose of PEG-IFN that results in a 50% inhibition of the viral production [23]. For case (i), we obtained $\varepsilon_{lead} = 0.95$ when choosing $D_{peg} = 180$ μg/week and $ED_{50} = 10$ μg/week estimated from patients who achieved SVR [23]. The infected cell death rate is generally higher in patients who attained SVR. We chose $\delta_{lead} = 0.18$ day^{-1} for the responder [23]. We also assumed that a drug resistant mutant, for example, T54A, pre-exists and confers 12-fold resistance to telaprevir and the relative fitness of drug-resistant to wild-type virus, f, is approximately 0.8 [24]. With these parameter values, triple therapy without lead-in reduces the total viral load more than the lead-in therapy during the first 4 wks (Fig. 1A1). However, for a simulated patient on lead-in, after telaprevir is added to the lead-in, viral load rapidly declines and by 7 wks both regimes achieve a very similar viral load reduction (Fig. 1A1). Because drug-resistant variants have a significantly reduced susceptibility to telaprevir ($\varepsilon^r_{total} \approx \varepsilon_{lead}$) [15, 25], immediate triple therapy has almost the same effect on drug-resistant virus as the lead-in therapy (Fig. 1A2). Further, because the telaprevir-resistant virus is sensitive to PEG-IFN [15, 25], drug resistance is successfully suppressed by both regimens in this case (Fig. 1A2).

For the partial responder, we plotted the total viral load change with and without a lead-in in Fig. 1B1 and the change of drug resistant virus in Fig. 1B2. To simulate a partial IFN responder, we chose a lower drug efficacy of the lead-in therapy, ε_{lead}=0.75, corresponding to ED_{50}=60 μg/week as observed in patients who did not achieve SVR [23], and a smaller infected cell death rate δ_{lead}=0.14 day^{-1} [17] than those used for the responder. Similar to

Fig. 1A, the initial viral decline is faster with immediate triple therapy than for the lead-in treatment, but becomes similar after telaprevir is added to the lead-in.

In Fig. 1C1, we plotted the total viral load change for a poor or null IFN responder assuming a further lower drug efficacy, ε_{lead}=0.6, (i.e., ED_{50}=120 μg/week [23]) and a further smaller infected cell death rate, δ_{lead}=0.1 day^{-1} [17, 18]. The predicted dynamics of both wild-type and drug resistant virus are illustrated in Fig. 1C2. Without adding telaprevir, the viral load is predicted to undergo a minor decrease and reach a steady-state level only slightly lower than the baseline (dotted line in Fig. 1C1). If telaprevir is included in the treatment, we predict that both therapies with and without a lead-in phase result in a similar viral breakthrough because of the emergence of drug resistance, except the breakthrough occurs later with the lead-in treatment (Fig. 1C2). This is not surprising in that telaprevir functionally acts like a monotherapy when the patient has a very limited response to IFN.

By explicitly incorporating the anti-HCV activity of RBV (Supplementary Eq. S1), we obtain similar predicted viral load changes in patients treated with and without a lead-in phase (Supplementary Fig. S1). When we also include the pharmacokinetic and pharmacodynamics of PEG-IFN-α-2a, we again predict similar responses with and without lead-in despite oscillations due to the weekly administration of PEG-IFN-α-2a (Fig. S2).

In the above simulations, we assumed that one nucleotide substitution could generate drug resistance to the protease inhibitor. This appears in genotype 1a patients treated with the protease inhibitors such as telaprevir, boceprevir, and danoprevir. For example, only one nucleotide change is required to generate the drug-resistant variant V36M (GTG to ATG) or R155K (AGG to AAG) [26, 27]. However, for genotype 1b, two nucleotide changes are needed to generate V36M (GTC to ATG) or R155K (CGG to AAG) [26, 27]. Thus, the probability of generating the same amino acid change for genotype 1b (μ^2) is much lower than for genotype 1a. With a baseline viral load $V_0 \approx 5\times10^6$ IU/ml, the drug resistant viral load (V_r) is about 10^{-2} IU/ml before therapy (the mutant frequency in the total virus population is approximately $\mu^2/(1-f)$ [28], where μ is assumed to be 2.5×10^{-5} per copied nucleotide [29] and the relative fitness f is assumed to be 0.8 [24]) and is likely to emerge during triple therapy. If a patient is treated with a period of lead-in therapy and the viral load is suppressed from 5×10^6 IU/ml to approximately 10^5 IU/ml by the lead-in, then the drug-resistant viral load will be approximately 10^{-4} IU/ml before addition of the protease inhibitor. A simple calculation from $(1-\varepsilon_{lead})p_r I_r \approx cV_r$ shows that the total number of cells infected by resistant virus after the lead-in is about 10 if we assume that infected cells can distribute throughout the 15 liter extracellular fluid in a 70 kg person. These infected cells may possibly be eradicated by stochastic effects. However, if the viral load can be suppressed to below 10^4 IU/ml by the lead-in, then the total number of cells infected by resistant virus is <1, which can be regarded as extinction before the protease inhibitor is added. Thus, the lead-in therapy may reduce the risk of resistance emergence in some genotype 1b patients in which two nucleotide changes are needed to generate resistance.

Discussion

We used a mathematical model to compare the predicted viral kinetics in patients treated with and without a lead-in phase. Because resistance is most likely to be seen when using a DAA for which a single mutation in its target can lead to resistance, we focused on analysis of this case using three representative in silico patients. The results showed that therapy with a lead-in phase followed by addition of a single DAA will achieve a similar viral load reduction or experience similar viral breakthrough as including the DAA from the beginning of therapy (Fig. 1). Thus, the current 4-wk P/R lead-in therapy followed by addition of a single protease inhibitor may not improve treatment outcomes. This prediction is consistent with the observations in recent clinical trials [5, 6]. For example, in the SPRINT-1 trial [5, 13], the overall percentage of patients attaining SVR was not significantly higher in patients who received the lead-in treatment than in those without lead-in. Likewise, no significant differences were found in the rates of virologic relapse and breakthrough [5] and similar boceprevir-resistant variants were identified in the lead-in and no-lead-in arms [13]. In the group with 28-wk treatment, genotype 1b patients treated with a lead-in achieved a lower SVR rate than without lead-in (60% vs. 70%) [5]. However, the difference is not significant (p=0.37). Furthermore, the SVR rates in these genotype 1b patients can be affected by the baseline HCV RNA level and other host factors. We also note that the mechanisms of RBV's action remain unclear and inclusion of RBV in combination with PEG-IFN and telaprevir was shown to be important in improving treatment responses [3, 30]. However, our model prediction should not be affected in that RBV is included in both regimes from the beginning of therapy.

Starting with a combination of PEG-IFN+RBV and a DAA reduces the viral load more substantially than the lead-in therapy initially (Fig. 1) and likely achieves higher rates of rapid virologic response (RVR, undetectable HCV RNA at wk 4 of treatment). However, the rate of early virologic response (EVR, undetectable HCV RNA at wk 12 of treatment) in the two groups with and without a 4-wk lead-in is expected to be similar (Fig. 1). This is in agreement with the data in [5]: the RVR rate in the group without lead-in was significantly higher than the group with lead-in (p<0.0001). However, the difference in the rate of EVR between lead-in and no-lead-in was not significant: p=0.53 for the group with 28-wk therapy (69% vs. 73%) and p=0.07 for the group with 48-wk therapy (77% vs. 68%).

If patients have no or very limited response to the IFN-based therapy, treatment with addition of a single protease inhibitor will very likely increase the risk of drug resistance and viral breakthrough because in such patients triple therapy is like a form of protease inhibitor monotherapy. In the study by McHutchison et al. [30], the majority of patients who had viral breakthrough during retreatment with a combination of telaprevir and P/R were nonresponders (undetectable HCV RNA levels never achieved during or at the end of the treatment period) to the prior P/R therapy. Lead-in therapy may have no or very little benefit of reducing the risk of developing drug resistance in these patients (however, it can help identify null responders as described below). Our simulation showed that in patients with null or limited response to IFN, the lead-in therapy resulted in a similar but delayed viral breakthrough as the no-lead-in therapy (Fig. 1C). Thus, we expect a similar SVR rate in treatment-experienced patients who are retreated with triple therapy including a protease

inhibitor with/without a lead-in phase. This is consistent with the data from the phase 3 REALIZE trial [6]. Two telaprevir-based treatment regimes with and without a 4-wk lead-in phase of P/R were used to retreat patients whose prior therapy was unsuccessful. Although immediate triple therapy achieved a significantly higher RVR rate ($p<0.0001$) than lead-in therapy (57% vs. 2%), the SVR rates were similar (64% vs. 66%) and no clinical benefit was found for lead-in in any of the subgroups of patients (null responders, partial responders, and relapsers) [6].

Unexpectedly, a lower SVR rate was reported in the lead-in groups of both treatment-experienced patients in the SILEN-C2 trial [11] and treatment-naive patients in the SILEN-C1 trial with the protease inhibitor faldaprevir [10] (Table 1). The underlying mechanisms for impaired treatment responses with the 3-day lead-in in these two studies are unknown. One possible reason could be that 3 days after the first dose of PEG-IFN-α-2a, PEG-IFN may not have sufficient antiviral effectiveness to prevent growth of some pre-existing drug resistant variants. For PEG-IFN-α-2a it usually takes 2–4 weeks until the maximum plasma concentration and full antiviral effectiveness is obtained [22]. Thus, giving faldeprevir after 3 days of lead-in therapy with P/R may increase the risk of drug resistance development and affect the treatment outcome in some patients. More detailed models [28, 31, 32] including multiple strains of drug resistant HCV and both forward and back mutations could potentially provide further insights. In any case, a lead-in therapy with 3-day P/R will not be incorporated into current and future clinical trials of this agent [10, 11].

We find the viral response to the IFN-based therapy plays an important role in predicting end-of-treatment response (Fig. 1). In this regard, a lead-in phase can be used to determine whether the addition of a DAA is needed or if treatment should be discontinued. If patients are very responsive to IFN, then the addition of a DAA may not be needed. Recent results suggest that the IL28B polymorphism is associated with spontaneous clearance after HCV infection [33] and is also a very strong baseline predictor of SVR to P/R [34]. Patients with the CC IL28B type have improved viral kinetics, reduced relapse rate, increased rates of RVR, EVR, and SVR [35, 36]. In a study of 233 treatment-naive genotype 1 patients with a low viral load at baseline ($<6\times10^5$ IU/ml), 48% achieved RVR after 4 wks of lead-in with P/R and did not have significant difference in the rate of SVR when they were further treated with P/R for 20 wks or P/R+boceprevir for 24 wks [37]. Thus, for CC IL28B patients or patients with a low baseline viral load who achieved RVR, addition of a single DAA may not be necessary and treatment duration may also be reduced [38]. This will prevent DAA-associated adverse effects, save costs, and avoid the risk of developing resistance. If patients are poor IFN responders (e.g., a decline in the HCV RNA level of <1 $\log_{10}$ IU/ml at wk 4), then adding a protease inhibitor to the treatment could lead to drug resistance. In the SPRINT-2 study [7], adding boceprevir to this subgroup achieved an SVR rate of 33%, but the success came at a cost; nearly half of the patients showed the development of boceprevir-resistant variants. Finally, response to lead-in in P/R treatment-experienced patients should also be considered to determine whether DAA-containing therapy can improve treatment outcomes. A recent sub-analysis of the REALIZE study [39] showed that after the 4-wk lead-in of P/R in patients who had ≥1 $\log_{10}$ decline from baseline HCV RNA versus <1 $\log_{10}$, SVR rates of 94% vs. 62% were achieved in prior relapsers, 59% vs. 56%

in partial responders, and 54% vs. 15% in null responders. The results suggest that in prior relapsers and partial responders there is no apparent benefit in accessing the response to P/R lead-in before starting telaprevir therapy. However, in prior null responders the response after lead-in may identify patients for whom telaprevir plus P/R could be suboptimal [39].

As more DAAs are approved, therapy with a combination of DAAs is possible [40–42]. We previously predicted that all double mutants may preexist before therapy in patients with a high baseline viral load of ~10^7 IU/ml [15]. Because of the presence of double mutants immediate therapy with two DAAs and P/R may not suppress drug resistance if each drug has a genetic barrier of only one mutation and the resistant variants are fit enough to grow. This might be the case if a protease inhibitor and non-nucleotide polymerase inhibitor were combined, as in the SOUND-C2 trial where patients were given faldaprevir (a protease inhibitor) and deleobuvir (a non-nucleoside polymerase inhibitor [42]. In this trial, 97% of patients with virological breakthrough (73 of 75 patients) had HCV variants with mutations in both NS3 and NS5B [42]. In a case such as this, a lead-in phase might have prevented the emergence of resistance in those patients that respond to P/R. In general, whether a drug resistant variant grows during therapy depends on its fitness relative to other variants [28]. Nucleotide polymerase inhibitors, such as sofosbuvir [43, 44], have not generated in vivo resistance presumably because the resistant variants are not fit enough to grow [45]. With agents of this type it seems that there would be no advantage of using a lead-in phase.

In summary, the current lead-in strategy with addition of a single protease inhibitor may not improve treatment outcomes, compared to immediate triple therapy. However, a period of P/R can identify IFN responders who may not need the addition of DAA(s) and null responders who will very likely develop drug resistance after addition of a protease inhibitor such as telaprevir or boceprevir. The viral kinetics during the lead-in period, combined with other factors such as the IL28B polymorphism, baseline viral load, and fibrosis, can be used to predict end-of-treatment response and help develop response-guided therapy for hepatitis C.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002; 347:975–982. [PubMed: 12324553]
2. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001; 358:958–965. [PubMed: 11583749]
3. Hezode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med. 2009; 360:1839–1850. [PubMed: 19403903]

4. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med. 2009; 360:1827–1838. [PubMed: 19403902]
5. Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet. 2010; 376:705–716. [PubMed: 20692693]
6. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011; 364:2417–2428. [PubMed: 21696308]
7. Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011; 364:1195–1206. [PubMed: 21449783]
8. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011; 364:1207–1217. [PubMed: 21449784]
9. Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med. 2011; 365:1014–1024. [PubMed: 21916639]
10. Sulkowski MS, Asselah T, Lalezari J, et al. Faldaprevir combined with peginterferon alfa-2a and ribavirin in treatment-naive patients with chronic genotype-1 HCV: SILEN-C1 trial. Hepatology. 2013; 57:2143–2154. [PubMed: 23359516]
11. Sulkowski MS, Bourliere M, Bronowicki J-P, et al. Faldaprevir combined with peginterferon alpha-2a and ribavirin in chronic HCV genotype-1 patients with prior nonresponse: SILEN-C2 trial. Hepatology. 2013; 57:2155–2163. [PubMed: 23504636]
12. Vierling J, Poordad F, Lawitz E, et al. Once daily narlaprevir (SCH 900518) in combination with peginterferon alfa-2b/ribavirin for treatment-naive patients with genotype-1 chronic hepatitis C: interim results from the NEXT-1 study. Hepatology. 2009; 50:90A.
13. Ogert RA, Howe JA, Vierling JM, et al. Resistance-associated amino acid variants associated with boceprevir plus pegylated interferon-alpha2b and ribavirin in patients with chronic hepatitis C in the SPRINT-1 trial. Antivir Ther. 2013; 18:387–397. [PubMed: 23406826]
14. Foster GR, Serfaty LD. Triple combination treatment for chronic hepatitis C with protease inhibitors, pegylated interferon and ribavirin: ‘lead-in or no lead-in’? Liver Int. 2012; 32 (Suppl 1): 61–63. [PubMed: 22212574]
15. Rong L, Dahari H, Ribeiro RM, Perelson AS. Rapid emergence of protease inhibitor resistance in hepatitis C virus. Sci Transl Med. 2010; 2:30ra32.
16. Lindenbach BD, Rice CM. Unravelling hepatitis C virus replication from genome to function. Nature. 2005; 436:933–938. [PubMed: 16107832]
17. Neumann AU, Lam NP, Dahari H, et al. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. Science. 1998; 282:103–107. [PubMed: 9756471]
18. Adiwijaya BS, Hare B, Caron PR, et al. Rapid decrease of wild-type hepatitis C virus on telaprevir treatment. Antivir Ther. 2009; 14:591–595. [PubMed: 19578245]
19. Foy E, Li K, Wang C, et al. Regulation of interferon regulatory factor-3 by the hepatitis C virus serine protease. Science. 2003; 300:1145–1148. [PubMed: 12702807]
20. Li K, Foy E, Ferreon JC, et al. Immune evasion by hepatitis C virus NS3/4A protease-mediated cleavage of the Toll-like receptor 3 adaptor protein TRIF. Proc Natl Acad Sci U S A. 2005; 102:2992–2997. [PubMed: 15710891]
21. 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]
22. Dahari H, Affonso de Araujo ES, Haagmans BL, et al. Pharmacodynamics of PEG-IFN-alpha-2a in HIV/HCV co-infected patients: Implications for treatment outcomes. J Hepatol. 2010; 53:460–467. [PubMed: 20561702]
23. Snoeck E, Chanu P, Lavielle M, et al. A comprehensive hepatitis C viral kinetic model explaining cure. Clin Pharmacol Ther. 2010; 87:706–713. [PubMed: 20463660]
24. Sarrazin C, Kieffer TL, Bartels D, et al. Dynamic hepatitis C virus genotypic and phenotypic changes in patients treated with the protease inhibitor telaprevir. Gastroenterology. 2007; 132:1767–1777. [PubMed: 17484874]

25. Kieffer TL, Sarrazin C, Miller JS, et al. Telaprevir and pegylated interferon-alpha-2a inhibit wild-type and resistant genotype 1 hepatitis C virus replication in patients. Hepatology. 2007; 46:631–639. [PubMed: 17680654]
26. Zhou Y, Bartels DJ, Hanzelka BL, et al. Phenotypic characterization of resistant Val36 variants of hepatitis C virus NS3-4A serine protease. Antimicrob Agents Chemother. 2008; 52:110–120. [PubMed: 17938182]
27. Zhou Y, Muh U, Hanzelka BL, et al. Phenotypic and structural analyses of hepatitis C virus NS3 protease Arg155 variants: sensitivity to telaprevir (VX-950) and interferon alpha. J Biol Chem. 2007; 282:22619–22628. [PubMed: 17556358]
28. Rong L, Ribeiro RM, Perelson AS. Modeling quasispecies and drug resistance in hepatitis C patients treated with a protease inhibitor. Bull Math Biol. 2012; 74:1789–1817. [PubMed: 22639338]
29. Ribeiro RM, Li H, Wang S, et al. Quantifying the diversification of hepatitis C virus (HCV) during primary infection: estimates of the in vivo mutation rate. PLoS Pathog. 2012; 8:e1002881. [PubMed: 22927817]
30. McHutchison JG, Manns MP, Muir AJ, et al. Telaprevir for previously treated chronic HCV infection. N Engl J Med. 2010; 362:1292–1303. [PubMed: 20375406]
31. Adiwijaya BS, Herrmann E, Hare B, et al. A multi-variant, viral dynamic model of genotype 1 HCV to assess the in vivo evolution of protease-inhibitor resistant variants. PLoS Comput Biol. 2010; 6:e1000745. [PubMed: 20419154]
32. Adiwijaya BS, Kieffer TL, Henshaw J, et al. A viral dynamic model for treatment regimens with direct-acting antivirals for chronic hepatitis C infection. PLoS Comput Biol. 2012; 8:e1002339. [PubMed: 22241977]
33. Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature. 2009; 461:798–801. [PubMed: 19759533]
34. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009; 461:399–401. [PubMed: 19684573]
35. Stattermayer AF, Stauber R, Hofer H, et al. Impact of IL28B genotype on the early and sustained virologic response in treatment-naive patients with chronic hepatitis C. Clin Gastroenterol Hepatol. 2011; 9:344–350. [PubMed: 20728570]
36. Thompson AJ, Muir AJ, Sulkowski MS, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. Gastroenterology. 2010; 139:120–129. [PubMed: 20399780]
37. Pearlman BL, Ehleben C. Hepatitis C genotype 1 virus with low viral load and rapid virologic response to peginterferon/ribavirin obviates a protease inhibitor. Hepatology. 2013 Accepted article. 10.1002/hep.26624
38. Dahari H, Cotler JS. Individualized treatment for patients with low HCV load (genotype 1): A viral kinetic approach. Hepatology. 2013 Accepted.
39. Foster GR, Zeuzem S, Andreone P, et al. Sustained virologic response rates with telaprevir by response after 4 weeks of lead-in therapy in patients with prior treatment failure. J Hepatol. 2013; 58:488–494. [PubMed: 23183521]
40. Olsen DB, Davies ME, Handt L, et al. Sustained viral response in a hepatitis C virus-infected chimpanzee via a combination of direct-acting antiviral agents. Antimicrob Agents Chemother. 2011; 55:937–939. [PubMed: 21115793]
41. Gane EJ, Roberts SK, Stedman CA, et al. Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose-escalation trial. Lancet. 2010; 376:1467–1475. [PubMed: 20951424]
42. Zeuzem S, Soriano V, Asselah T, et al. Faldaprevir and deleobuvir for HCV genotype 1 infection. N Engl J Med. 2013; 369:630–639. [PubMed: 23944300]
43. Gane EJ, Stedman CA, Hyland RH, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med. 2013; 368:34–44. [PubMed: 23281974]

44. Osinusi A, Meissner EG, Lee YJ, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. JAMA. 2013; 310:804–811. [PubMed: 23982366]

45. Wohnsland A, Hofmann WP, Sarrazin C. Viral determinants of resistance to treatment in patients with hepatitis C. Clin Microbiol Rev. 2007; 20:23–38. [PubMed: 17223621]

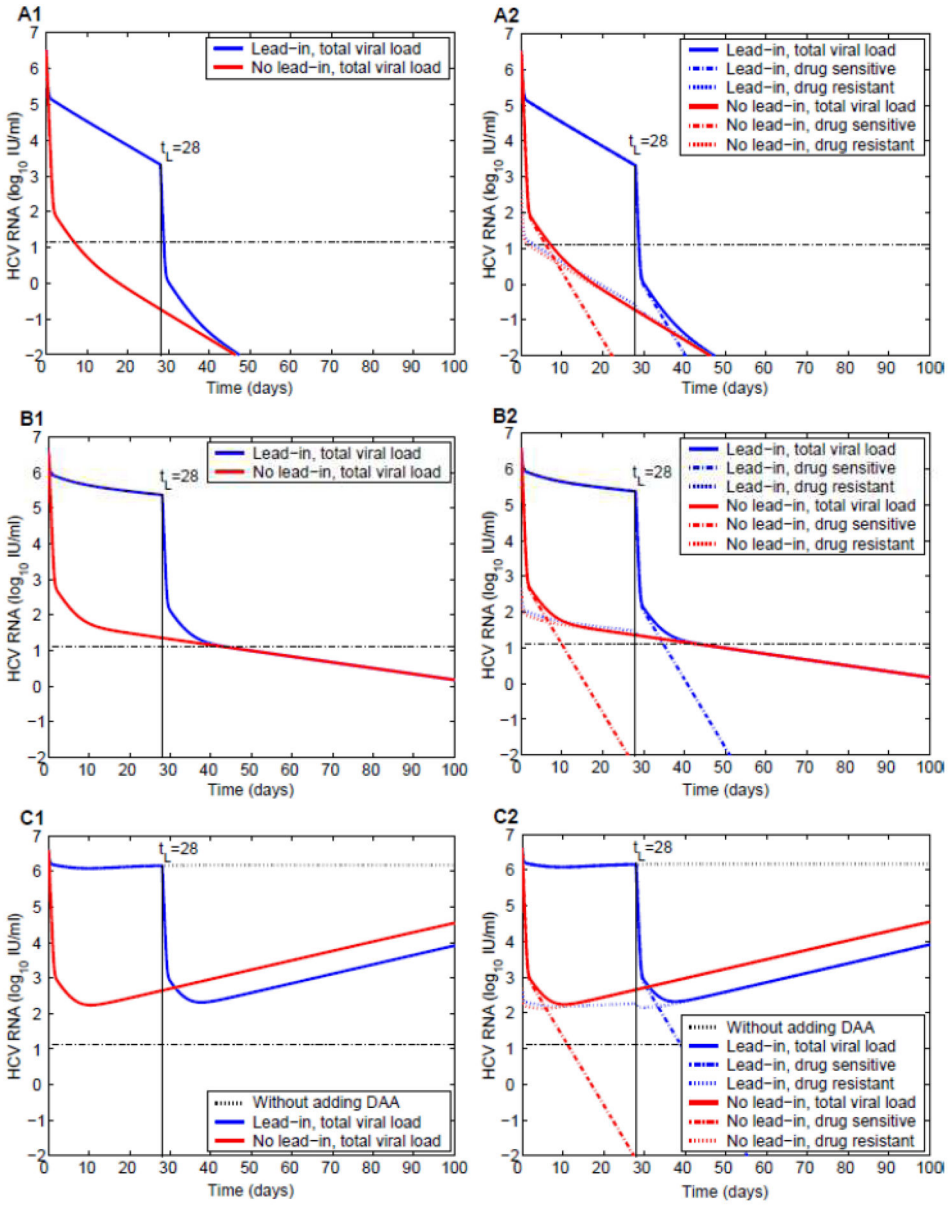

Figure 1. Predicted viral kinetics in patients treated with and without a lead-in phase

The left panel shows the total viral load change while the right panel shows the changes of both wild-type and drug resistant virus. **A1** and **A2**: Patient who is very responsive to the lead-in therapy. Parameters are chosen from [15, 23]: s=0, d=0.01 day^{-1}, β=5×10^{-8} ml/(virion·day), δ_{DAA}=0.44 day^{-1}, μ=2.5×10^{-5} per copied nucleotide, T_{max}=1.3×10^{7} cells/ml, $N=T_{max}/2$, ρ=1 day^{-1}, ε^{s}_{DAA}=0.999, ε^{r}_{DAA}=0.01, c=6.2 day^{-1}, p_s=10 virions/(cell·day), $f=p_r/p_s$=0.8, ε_{lead}=0.95, and δ_{lead}=0.18 day^{-1}. **B1** and **B2**: Patient who is a partial responder to the lead-in therapy. Parameters used are the same as those in (A) except ε_{lead}=0.75 and δ_{lead}=0.14 day^{-1}. **C1** and **C2**: Patient who is a poor or null responder to the lead-in therapy. Parameters used are the same as those in (A) except ε_{lead}=0.6 and δ_{lead}=0.1 day^{-1}. The horizontal dash-dotted line represents the detection limit (15 IU/ml [5]).

Table 1

Summary of available data from clinical trials with a lead-in phase

Clinical trials [a]	Treatment	RVR	EVR	Viral breakthrough	Viral relapse	SVR
SPRINT-1 [b] (treatment-naive patients)	Lead-in: PR4+PRB24 (n=103)	3%	69%	4%	24% (18/76)	56% (58/103, overall) 51% (27/53, 1a) 60% (22/37, 1b)
	No lead-in: PRB28 (n=107)	39%	73%	7%	30% (24/81)	54% (58/107, overall) 51% (34/67, 1a) 70% (21/30, 1b)
	Lead-in: PR4+PRB44 (n=103)	9%	77%	5%	3% (2/79)	75% (77/103, overall) 72% (43/60, 1a) 83% (29/35, 1b)
	No lead-in: PRB48 (n=103)	37%	68%	12%	7% (5/73)	67% (69/103, overall) 58% (32/55, 1a) 83% (30/36, 1b)
REALIZE [c] (treatment-experienced patients)	Lead-in: PR4+PRT12+PR32 (n=264)	2% (4/264, overall) 0 (0/75, null responder) 0 (0/48, partial responder) 3% (4/141, relapser)			13% (27/210, overall) 25% (9/36, null responder) 25% (9/36, partial responder) 7% (9/138, relapser)	66% (175/264, overall) 33% (25/75, null responder) 54% (26/48, partial responder) 88% (124/141, relapser)
	No lead-in: PRT12+PR36 (n=266)	57% (152/266, overall) 26% (19/72, null responder) 65% (32/49, partial responder) 70% (101/145, relapser)			13% (26/204, overall) 27% (8/30, null responder) 21% (8/39, partial responder) 7% (10/135, relapser)	64% (171/266, overall) 29% (21/72, null responder) 59% (29/49, partial responder) 83% (121/145, relapser)
SILEN-C1 [d] (treatment-naive patients)	Lead-in: PR3d+PRF24+PR24 (n=143)	78%		6%	11%	72%
	No lead-in: PRF24+PR24 (n=146)	87%		4%	8%	84%
SILEN-C2 [e] (treatment-experienced patients)	Lead-in: PR3d+PRF24+PR24 (n=142)	43%		30%	27%	28% (40/142, overall) 21% (12/56, null responder) 31% (17/54, partial responder)
	No lead-in: PRF24+PR24 (n=76)	45%		36%	12%	41% (31/76, overall) 35% (14/40, null responder) 50% (13/26, partial responder)

[a]The clinical trials SPRINT-2 [7] and RESPOND-2 [8] are not included in the table because a 4-wk lead-in therapy with P/R was administered to all groups of patients. There is no comparison between the lead-in therapy followed by addition of boceprevir and immediate triple therapy.

[b] In the SPRINT-1 study [5], boceprevir (800 mg TID) was given with/without a 4-wk lead-in therapy (PEG-IFN-α-2b 1.5 μg/kg + RBV 800–1400 mg/day) to treatment-naive patients with genotype 1 HCV infection. The detection limit (Roche Cobas TaqMan) is 15 IU/ml. RVR (EVR): undetectable HCV RNA on or before 4 (12) wks of treatment. Viral breakthrough: persistent ≥ 2 $\log_{10}$ increase from nadir and ≥ 50,000 IU/ml. Viral relapse: detectable HCV RNA at end of follow-up in patients who were undetectable at end of treatment.

[c] In the phase 3 REALIZE trial [6], telaprevir with P/R was used to treat patients with prior unsuccessful therapy. Lead-in group: 4 wks of P/R followed by 12 wks of telaprevir (750 mg, Q8H) and P/R, followed by 32 wks of P/R; No-lead-in group: 12 wks of telaprevir (750 mg, Q8H) and P/R, followed by 36 wks of P/R. Null responder: a patient who achieved < 2 $\log_{10}$ reduction in HCV RNA at wk 12 of a prior P/R therapy. Partial responder: a patient who achieved at least 2 $\log_{10}$ viral load reduction at wk 12, but never had undetectable HCV RNA during the prior therapy. Relapser: a patient whose viral load was undetectable at the end of prior treatment but with subsequent virologic relapse.

[d] In the SILEN-C1 trial [10], faldaprevir (240 mg QD) was given to treatment-naive patients with/without a 3-day lead-in therapy (PEG-IFN-α-2a 180 μg/wk + RBV 1000–1200 mg/day). RVR: HCV RNA below limit of quantification (< 25 IU/ml) at wk 4. Viral breakthrough: increase in HCV RNA by ≥ 1 $\log_{10}$ from nadir during treatment or confirmed increase in HCV RNA ≥ 100 IU/ml if nadir was undetectable. Relapse: HCV RNA undetectable at the end of treatment but detectable during the follow-up period.

[e] In the SILEN-C2 trial [11], faldaprevir (240 mg QD) was given to treatment-experienced patients with/without a 3-day lead-in therapy (PEG-IFN-α-2a 180 μg/wk + RBV 1000–1200 mg/day).