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BRIEF REPORT

Modeling-Based Response-Guided DAA Therapy for Chronic Hepatitis C to Identify Individuals for Shortening Treatment Duration

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Shortening duration of direct-acting antiviral therapy for chronic hepatitis C could provide cost savings, reduce medication exposure, and foster adherence and treatment completion in special populations. The current analysis indicates that measuring hepatitis C virus at baseline and on days 7 and 14 of therapy can identify patients for shortening therapy duration.

Keywords. direct-acting antivirals; hepatitis C virus; mathematical modeling; response-guided therapy; time to cure.

The advent of all-oral direct-acting antivirals (DAAs) has transformed the landscape of hepatitis C virus (HCV) therapy and paved the path to the ambitious World Health Organization goal of viral hepatitis elimination by 2030 [1]. However, several remaining challenges such as DAA cost and treatment of HCV in special populations must be overcome to achieve this goal [2, 3]. Shortening duration of DAA therapy could provide cost savings [4–7], reduce medication exposure (eg, during pregnancy [8]), and help to foster adherence and treatment completion in general [9] and specifically in special populations (eg, people who inject drugs [2] and incarcerated individuals [10]), which is key to achieving cure [11]. Thus, identifying individuals for shortening DAA therapy duration is warranted.

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We recently reported a proof-of-concept study [12] demonstrating that real-time (ie, on treatment) mathematical modeling–based (Figure 1A) response-guided therapy (RGT) with DAA for chronic HCV infection can be utilized for shortening DAA duration without compromising treatment efficacy. The proof-of-concept study [12] relied on measuring HCV at baseline and on days 2, 7, 14, and 28 after initiation of DAA therapy, which is cumbersome in clinical practice. We also reported [12] that all patients (but 1) in whom viral load was reduced to <14 IU/mL at day 14 after initiation of treatment were predicted to reach cure on a shortened duration of DAA therapy, suggesting that measuring viral load at day 28 may not be needed.

As reducing the number of HCV measurements would facilitate large-scale implementation of the RGT approach, we aim in the current study to retrospectively investigate whether some HCV measurement time points in the proof-of-concept study (ie, days 2, 7, 14, and/or 28) can be excluded without compromising the ability to predict the DAA therapy duration needed to reach cure.

METHODS

Mathematical Model

The typical HCV RNA decline pattern on DAA therapy is biphasic and consists of a first rapid viral decline phase, lasting ~1–2 days, followed by a slower second phase decline [5, 13]. Thus, the standard biphasic model (Figure 1A) [14] was used:

$$\frac{dI}{dt} = \beta V T_0 - \delta I$$
$$\frac{dV}{dt} = (1-\varepsilon) pI - cV, \quad (1)$$

where T_0 represents the number of susceptible target cells, I the number of infected cells, and V the HCV level in blood. HCV (V) infects $T_0$with the rate constant β, generating infected cells (I), which produce V at rate of p per infected cell. Infected cells are lost at a rate of δ per infected cell, and virions are assumed to be cleared from blood at a rate of c per virion. DAA efficacy, ε, in blocking viral production from infected cells is assumed to be between 0 and 1 (where 1 = 100% efficacy).

Initial Parameter Estimations

Similar to our proof-of-concept study [12], we assumed that the T_0 level remained constant during DAA therapy. The pretreatment (time, t = 0) infected cell level $I(0)$ is represented by the steady state pretreatment level of $I(0) = \frac{\beta T_0 V(0)}{\delta}$, where $V(0)$ is

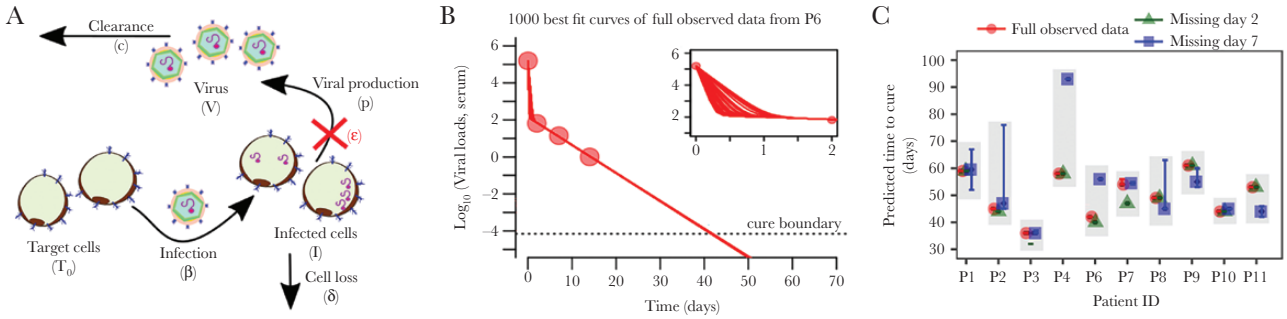

Figure 1. Modeling time to cure of hepatitis C on DAA therapy. A, Schematics representing HCV life cycle: The model (Equation 1) assumes a fixed target cell population ($T0$) that becomes infected at rate β, whereas infected cells (I) are lost at a rate of δ. Moreover, infected cells produce viral progeny at a rate of p per infected cell, and HCV virus (V) in the serum clears at a rate of c. DAA inhibits viral production (p) with efficacy ε. B, Predictions of the time to cure from best fit estimates of parameters (c, δ, and ϵ) using observed data from individual P6 reported in Etzion et al. [12], showcasing that TTC is accurately predicted despite nonidentifiability in estimated parameters (Supplementary Figure 1B). C, Median (symbols), minimum and maximum (vertical lines) modeling predicted TTC in 10 individuals from our proof-of-concept study (in whom real-time modeling was used to shorten DAA therapy) [12], using all measured data points (red) or excluding either day 2 (green) or day 7 (blue) viral samples (min and max TTC values are provided in Table 1). Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; TTC, time to cure.

the pretreatment measured viral load of each patient. The viral production rate constant was set to pretreatment level $p = \frac{cV(0)}{I(0)}$. We previously showed [14, 15] that Equation 1 can be solved analytically independently ofβ, p, andT_0. Therefore, we arbitrarily fixed $\beta = 3.5 \times 10^{-9}$mL/virion/d and $T_0 = 1 \times 10^7$ cells/mL.

Time to Cure

As previously done [4–6, 12, 16–20], time to cure (TTC) was defined as the time to reach <1 HCV particle in the entire extracellular body fluid. For example, a value of 1 virus copy in 15 L of extracellular body fluid volume, that is, $V = 7 \times 10^{-5}$ IU/mL, was used as the threshold for cure.

Model Fitting Procedure

The biphasic model (Equation 1) was fitted using the Levenberg-Marquardt algorithm embedded in the function "lsqnonlin" in Matlab R2021a (The Mathworks, Natick, MA, USA), with the measured HCV kinetic data obtained from the 10 patients in the proof-of-concept study [12] for whom the model was applied during treatment to shorten standard DAA therapy. Live Matlab scripts are provided in Churkin et al. [21].

Starting with different initial guesses for each unknown parameter (c, δ, and ϵ), the fitting procedure consisted of finding 1000 model parameter sets of best fits ($c \in [1,\ 25]/day$, $\delta \in [0.1,\ 1.5]/day$, and $\epsilon \in [0.90,\ 0.9999]$) and recording corresponding goodness of fit using corrected Akaike Information Criteria (AIC_c) [22]. The duration of the first viral decline phase and TTC were estimated (Figure 1B). In the final step, we only accepted TTC from those best fits that were within 2 points of the lowest AIC_c and those with a duration of the first phase ≤2.5 days. The first data point below detection or below the lower limit of quantification was assigned a value ($\in [0.2,\ 15]$IU/mL). We explored removing day 28 and either day 2 or day 7 from the 10 patients and repeated the same procedure, projecting TTC using truncated data.

Linear Regression Procedure

We also explored using linear regression (ie, lm function in R) to predict TTC using only HCV measurements on days 7 and 14.

Patient Consent

The study was approved by the institutional review boards of Soroka and Rabin Medical Centers and was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. All patients provided written informed consent.

RESULTS

We first confirmed that TTC for each of the 10 patients, using all the measured data points, was in agreement with the estimated TTC reported in Table 1 [12]. In 2/10 patients (P8 and P9), HCV at day 28 was detected and was used for predicting TTC as in Etzion et al. [12]. Excluding day 28 in these 2 patients had a limited effect on TTC projections, leading to underprediction by 2 days in P8 and overprediction by 6 days in P9 (Table 1).

Further excluding the day 2 HCV measurement had a limited effect on maximum TTC projections (Figure 1B vs Supplementary Figure 1A), which remained accurate in 8/10 cases (Figure 1C, Table 1). In 2 patients (P3 and P7), this strategy led to underprediction by 4 and 8 days, respectively (Table 1). In contrast, excluding day 7 disproportionality affected the maximum TTC projections, resulting in over- or underprediction by at least 1 week in 6 individuals (Figure 1C) and overprediction by about 5 weeks in 2 additional patients (P2 and P4) (Table 1). Interestingly, applying linear regression using only day 7 and day 14 measurements for estimating TTC

Table 1. Predicted TTC in 10 Individuals From the Proof-of-Concept Study [12]

Patient	Proof-of-Concept Study	Modeling Full Observed Data (Scenario I)	Modeling Excluding Day 2 (Scenario II)	Linear Regression Using Only Days 7 and 14 (Scenario III)	Modeling Excluding Day 7 (Scenario IV)
P1	59	59 [59, 59]	59 [59, 59]	59	60 [52, 67]
P2	46	45 [45, 45]	44 [44, 44]	44	47 [45, 76]
P3	36	36 [36, 36]	27 [26, 32]	NA	36 [36, 37]
P4	56	58 [58, 58]	58 [58, 58]	57	93 [93, 93]
P6	43	42 [42, 42]	40 [40, 40]	39	56 [56, 56]
P7	55	54 [54, 56]	47 [47, 47]	47	55 [54, 55]
P8[a]	53	51 [50, 54] **49 [49, 49]**	54 [53, 54] **49 [49, 49]**	48	55 [55, 55] **45 [45, 63]**
P9[a]	56	55 [55, 57] **61 [61, 61]**	57 [57, 57] **61 [61, 61]**	60	56 [56, 56] **55 [53, 60]**
P10	44	44 [44, 44]	44 [44, 44]	43	45 [45, 45]
P11	53	53 [53, 53]	53 [53, 53]	52	44 [42, 46]

The TTC estimates are reported as median [minimum, maximum] in 3 scenarios: (i) fitting Equation 1 with fully observed data, (ii) fitting Equation 1 while removing day 2, and (iii) Fitting Equation 1 while removing day 7.

Abbreviations: HCV, hepatitis C virus; NA, could not be done as day 7 was missing in P3; TTC, time to cure.

[a]Two patients (of 10) in whom day 28 HCV viral load was detected who were used for modeling TTC prediction in the proof-of-concept study. TTC estimates in bold indicate estimates excluding day 28.

agreed with the TTC estimated by fitting the model (Equation 1) excluding day 2 (Table 1) in all but 1 case (P3, for whom linear regression could not be employed due to a missing day 7 measurement).

DISCUSSION

In the current study, we retrospectively modeled proof-of-concept trial data to further examine whether some monitoring time points may be removed without affecting TTC prediction. Modeling results indicated that on-treatment day 2 and day 28 clinical visits may not be necessary as their exclusion had a limited impact on TTC predictions. In a minority of cases, however, this strategy led to underprediction by at most 8 days, the impact of which can be offset by a precautionary 1-week extension of the predicted TTC. In contrast, missing day 7 measurement disproportionality affected the maximum TTC projections, resulting in over- or underprediction by at least 1 week in 6 individuals. A possible explanation for the importance of the day 7 measurement over day 2 is that days 7 and 14 constitute the *final* phase of viral decline (ie, the second phase in the biphasic model), whereas day 2 could be part of a *transient* phase that precedes the final phase, as we previously reported [23]. Thus, day 7 and day 14 measurements play a key role in predicting TTC.

Applying linear regression on only day 7 and day 14 measurements also predicted TTC accurately in all patients but 1 (P3), in whom day 7 measurement was missing. As the modeling approach (Equation 1) included the pretreatment measured viral load, it was still possible to predict TTC in P3 without day 7 (Table 1). In addition, linear regression could lead to overestimation of TTC compared with the modeling-based approach, as shown for a hypothetical patient in Supplementary Figure 2. These examples highlight the limitations of using linear regression to predict TTC based on viral measurements at days 7 and 14 and support the use of modeling to make TTC predictions.

Three parameters (c, δ, and ϵ) were estimated for each patient to predict TTC. The general rule of thumb in the parameter estimation procedure dictates that more data points than the number of estimated parameters are needed [24]. As we aim to minimize the number of on-treatment HCV measurements to 3 (ie, baseline, days 7 and 14), the 3 viral kinetic parameters (c, δ, and ϵ) cannot be estimated with confidence (nonidentifiability issues), as shown for a representative case (P6 in Supplementary Figure 1B). However, despite these nonidentifiability issues, the overarching goal of accurately predicting TTC remains largely unaffected (Figure 1B; Supplementary Figure 1A).

CONCLUSIONS

The current analysis indicates that on-treatment day 2 and day 28 HCV measurements are not critical for predicting TTC. Measuring HCV at baseline and on days 7 and 14 after initiation of DAA therapy provides a simplified and more practical on-treatment monitoring procedure during modeling-based RGT that can be readily adopted in clinical practice. Further validation in a large-scale clinical trial will support the routine implementation of our individualized treatment approach in patients receiving DAA for chronic hepatitis C.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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CRediT authorship contributions. Ashish Goyal: formal analysis, investigation, writing—original draft. Alex Churkin: software, writing—review & editing. Danny Barash: methodology, writing—review & editing. Scott J. Cotler: funding, methodology, writing—review & editing. Amir Shlomai: conceptualization, methodology, data curation, writing—review & editing. Ohad Etzion: conceptualization, methodology, data curation, writing—review & editing. Harel Dahari: conceptualization, supervision, funding, methodology, writing—original draft, writing—review & editing.

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