

Modeling Viral and Drug Kinetics: Hepatitis C Virus Treatment with Pegylated Interferon Alfa-2b

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ABSTRACT

Administration of peginterferon alfa-2b plus ribavirin results in an early hepatitis C virus (HCV) RNA decay followed by an increase as the drug concentration declines between doses. Upon administration of the next dose 1 week later, the same pattern is observed. We have incorporated pharmacokinetic/pharmacodynamic analysis into a model of viral dynamics to describe the effect that changes in drug concentration and effectiveness can have on viral levels. To illustrate the relationship between pharmacokinetics and viral dynamics, we fit the model to data from four HCV/human immunodeficiency virus co-infected patients, and obtained good agreement with the measured serum HCV RNA levels. We were able to account for the observed increases in HCV RNA, and estimate virion and drug half-lives that are in agreement with previous reports. Models incorporating pharmacokinetics are needed to correctly interpret viral load changes and estimate drug effectiveness in treatment protocols using peginterferon alfa-2b.

KEYWORDS: PEG-IFN, pharmacokinetics, modeling, HCV, viral dynamics

The delayed clearance of peginterferon alfa-2b (PEG-IFN alfa-2b) from the body allows it to be dosed once weekly in HCV patients, less frequently than the usual dosing of three times a week for standard IFN alfa.^{1,2} While once-weekly dosing results in greater convenience for patients, it leads to decreases in drug concentration between doses, resulting in decreases in efficacy and increases in viral load as drug concentrations drop.³ The effects of the decrease in drug concentration on HCV RNA have not been explored. Explanation of the interplay among these phenomena requires a combination of pharmacokinetic, pharmacodynamic, and viral dynamic models. In this article, we illustrate these principles and present a new theoretical framework to de-

scribe the antiviral effectiveness of treatment with PEG-IFN alfa-2b plus ribavirin.

VIRAL LOAD DURING TREATMENT WITH PEGYLATED INTERFERON ALFA-2B

We conducted a preliminary analysis of 4 HCV-infected patients treated with 1.5 $\mu\text{g}/\text{kg}$ PEG-IFN alfa-2b (12 kDa) once weekly plus daily ribavirin (13 mg/kg) for 28 days. Three of the 4 patients were male, 3 were infected with genotype 1a and one with genotype 2, 2 patients were White, one was Hispanic, and one was African American (Table 1). The average patient age was 51 years, and average baseline weight was 86 kg (Table 1). These

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Table 1 Patient Demographics

Patient	Age (years)	Sex	Race	Weight (kg)	HCV Genotype
1	56	M	Caucasian	81.7	1a
2	46	M	Hispanic	88.9	1a
3	48	F	African-American	81.6	1a
4	52	M	Caucasian	93.4	2
Average (\pm SD)	50.5 \pm 4.4			86.4 \pm 5.8	

patients were also co-infected with human immunodeficiency virus (HIV)-1 and had HIV-1 RNA levels below the limit of detection of 400 copies/mL. Serum HCV RNA was measured when the first, second, third, and fifth doses were given, and at regular intervals between doses. We analyzed the viral dynamics during the first week, when sampling was most frequent: at baseline, at 6 and 12 hours after baseline, and on days 1, 2, 3, 5, 6, and 7 after baseline. In patient #3, no measurements were taken on days 2 and 3, but a measurement was taken on day 4.

The intensive sampling schedule around the weekly doses of PEG-IFN alfa-2b allowed the characterization of HCV dynamics as the serum concentration

of PEG-IFN alfa-2b peaked and waned.³ In most patients, there was an initial fast pronounced decline in HCV RNA following the first dose, the same as had been observed in previous studies of HCV treatment.⁴⁻⁸ A few days after the first dose, most of the patients exhibited a rebound in HCV RNA (Fig. 1). We hypothesize that this rebound resulted from a decline in drug levels and, consequently, in drug effectiveness.

MODELING OF VIRAL DYNAMICS

The Neumann et al⁴ model of viral dynamics is described by the following set of differential equations for infected cells and free virus:

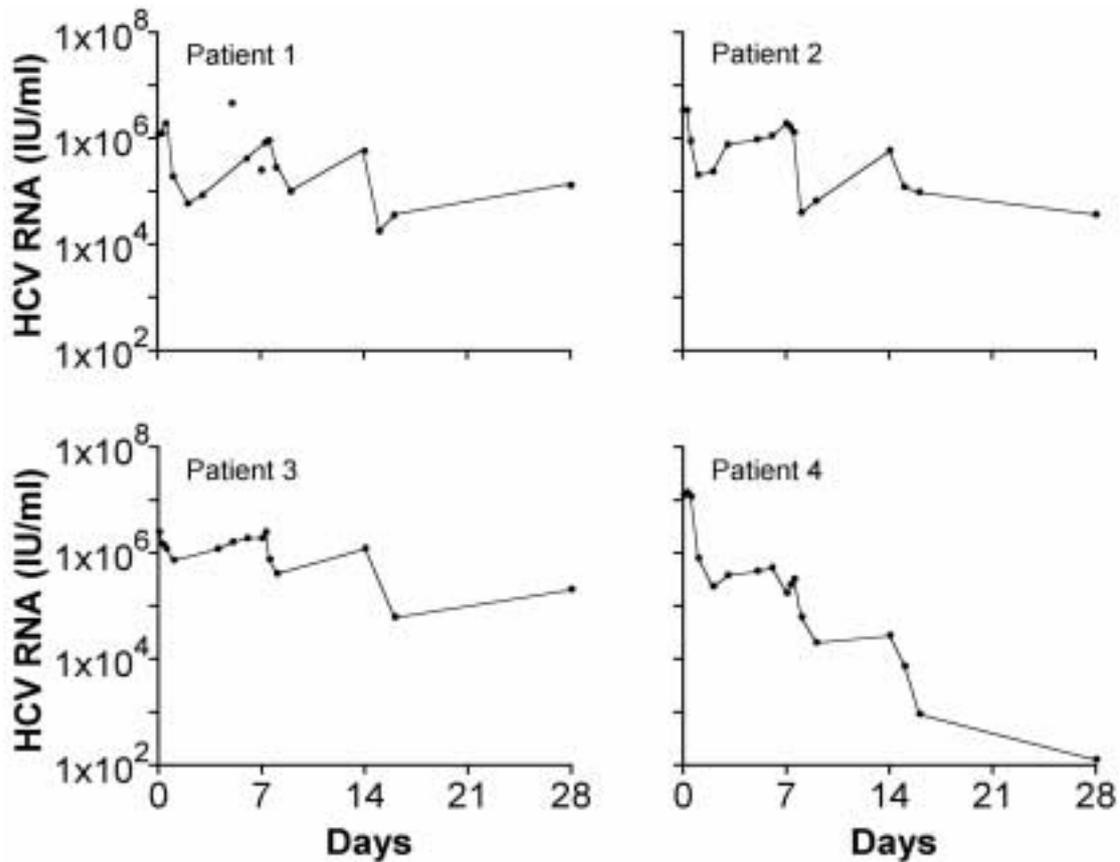


Figure 1 Evolution of serum HCV RNA levels during successive administration of PEG-IFN alfa-2b injections in 4 individuals infected with HCV and HIV.

$$\begin{aligned} dI/dt &= \beta VT - \delta I \\ dV/dt &= (1 - \epsilon(t)) pI - cV \end{aligned} \quad (1)$$

In this system, the free virus, V , infects uninfected hepatocytes (the βVT term), thereby generating infected cells, I , that subsequently produce virus at rate p per cell. The virus is cleared with rate constant c and infected cells are lost at rate δ per cell. PEG-IFN alfa-2b is assumed to block a fraction, $\epsilon(t)$, of the production of virus from infected cells but not to affect virion or infected cell clearance rates. To solve these equations, we assume that the number of uninfected cells, T , remains approximately constant during therapy.

When drug effectiveness is constant, that is, $\epsilon(t) = \epsilon$, these equations can be solved to yield the solution, Equation 2, which predicts that viral load $V(t)$ will decrease with (time on therapy, t).

$$V(t) = \frac{1}{2} V_0 \left[\left(1 - \frac{c + \delta - 2\epsilon c}{\theta} \right) e^{-\lambda_1(t-t_0)} + \left(1 + \frac{c + \delta - 2\epsilon c}{\theta} \right) e^{-\lambda_2(t-t_0)} \right], \quad (2)$$

where

$$\begin{aligned} \lambda_1 &= 0.5(c + \delta + \theta), \lambda_2 = 0.5(c + \delta - \theta), \text{ and} \\ \theta &= \sqrt{(c - \delta)^2 + 4(1 - \epsilon)c\delta}. \end{aligned}$$

If $c \gg \delta$, then $\lambda_1 \sim c$ and $\lambda_2 \sim \epsilon\delta$, corresponding to the first and second phase slopes observed when $\ln V(t)$ is plotted against t . Additionally, the virus is initially assumed to be in steady state, so that V_0 represents a constant baseline amount of HCV RNA. The parameter t_0 describes the delay usually observed between the administration of IFN and its effect in blocking virion production, which causes the initial decline in viral load. When a delay is present, Equation 2 is valid following the delay (i.e., for $t > t_0$), and for $t < t_0$, $V(t) = V_0$. While V_0 and t_0 can be roughly estimated directly from the data, here we used nonlinear least-squares regression analysis to fit the first 7 days of viral load data to Equation 2 to estimate V_0 and t_0 . These values (Table 2) were used in the analyses that follow.

Modeling of Pharmacokinetics— Elimination-Only Model

While Equation 2 has been shown to accurately fit viral load data obtained when patients are treated daily with high-dose standard IFN,⁴⁻⁶ it is not appropriate to describe the changes in viral load when PEG-IFN alfa-2b is given once weekly. With once-weekly dosing there appears to be a reduction in the drug's effectiveness in blocking viral production due to a decline in its concentration between doses,³ and hence the assumption of constant drug effectiveness no longer applies. If we assume that after the delay t_0 , the concentration of PEG-IFN alfa-2b simply decays exponentially, the drug concentration, C , over time can be described by

$$C(t) = C_0 e^{-k_e(t-t_0)}, \quad (3)$$

where C_0 is the drug concentration at time t_0 and k_e is the rate constant for drug elimination. Because effectiveness can be assumed to depend on drug concentration as⁹

$$\epsilon(t) = \frac{C(t)}{IC_{50} + C(t)}, \quad (4)$$

where IC_{50} is the concentration at which the drug's effectiveness is half its maximum, the decay in drug concentration described in Equation 3 leads to a decrease in effectiveness. Simulated changes in drug concentration and effectiveness, as predicted by this model, are displayed in Figure 2, where we assume that Equation 4 is valid for $t > t_0$.

Equations 3 and 4 were incorporated into Equation 1 to create a new model for viral load change under PEG-IFN alfa-2b treatment. The delay t_0 is interpreted as comprising both the time for the drug level to rise following injection as well as the biological delay between IFN binding to its cellular receptor and the antiviral response of the infected cell. Using nonlinear least-squares regression analysis, data from the first 7 days of treatment were fitted to this "elimination-only model" (Fig. 3). Values for the parameters c , δ , C_0/IC_{50} , and k_e were estimated, and the maximum effectiveness, that is,

Table 2 Parameter Estimates from Fitting the Elimination-Only Model

Patient	V_0 (10 ⁶ IU/mL)	δ (day ⁻¹)	c (day ⁻¹)	ϵ_{\max}	ϵ_{\min}	k_e (day ⁻¹)	t_0 (days)
1	1.39	0.37	4.20	0.99	0.03	1.11	0.50
2	3.34	0.25	5.39	0.98	0.02	1.10	0.25
3	2.34	0.02	1.76	0.89	0.07	0.66	0.00
4	12.8	0.45	9.16	0.98	0.63	0.45	0.64
Average (±SD)	5.0 ± 5.3	0.3 ± 0.2	5.1 ± 3.1	0.96 ± 0.05	0.2 ± 0.3	0.8 ± 0.3	0.4 ± 0.3

The virion production rate, p , was fixed at 10 virions/cell/day for all patients. V_0 and t_0 were estimated from fits of HCV RNA to Equation 2.

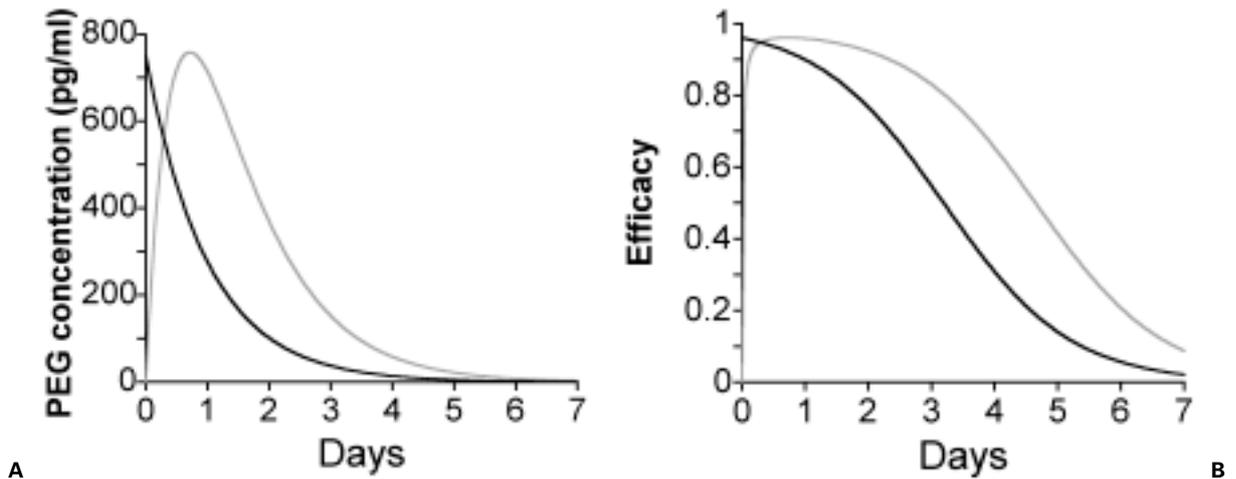


Figure 2 Simulated concentration and efficacy profiles with once-weekly dosing. Delays are not illustrated. Parameter values used in the simulations were: $k_a = 1.9 \text{ d}^{-1}$, $k_e = 1.0 \text{ d}^{-1}$, Dose = 129 μg , $IC_{50} = 30.96 \text{ pg/mL}$, $C_0 = 750 \text{ pg/mL}$, and $F/V_d = 0.012 \text{ L}^{-1}$. (A) Drug concentration over time; elimination-only model (black) and absorption and elimination model (grey). (B) Drug efficacy over time; elimination-only model (black) and absorption and elimination model (grey).

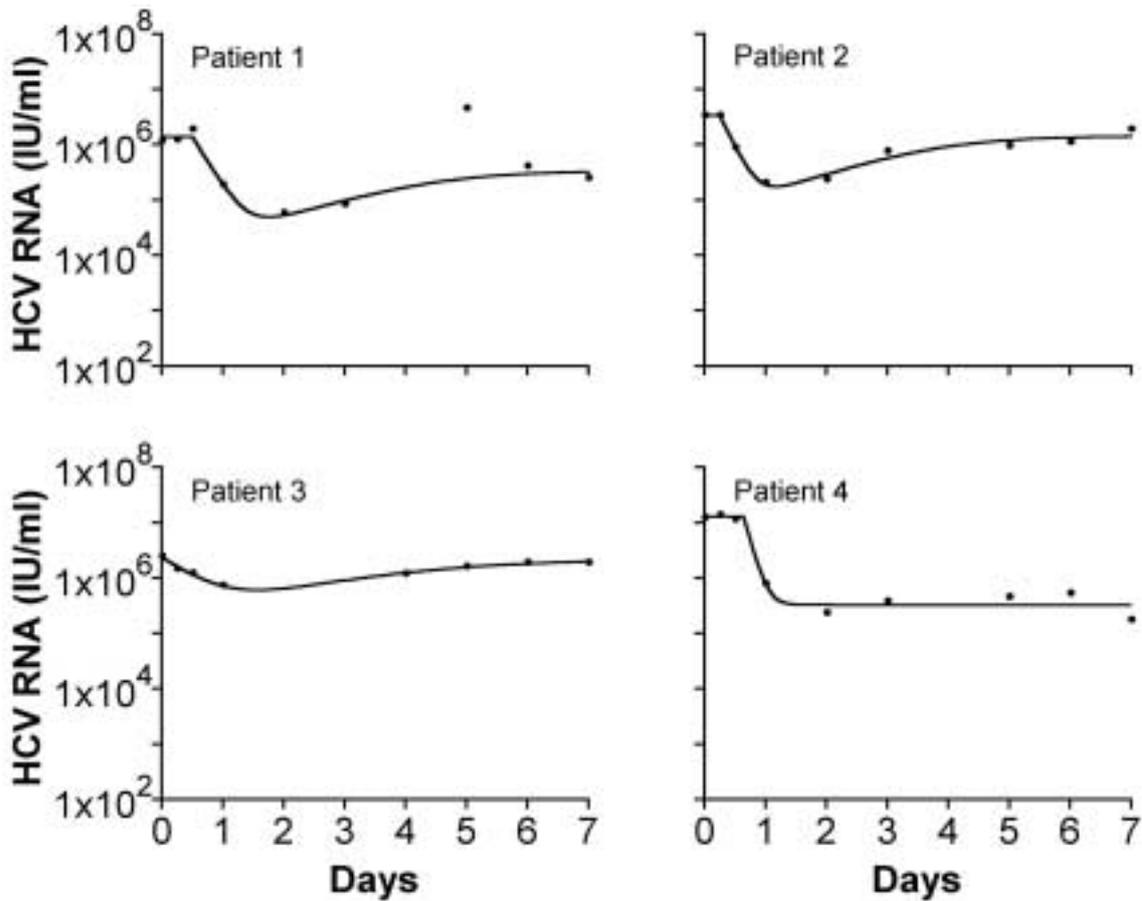


Figure 3 HCV RNA according to the elimination-only model. Best-fit solutions (solid line) of the model, Equations (1) – (4), to experimental data (●) from 4 patients during the first 7 days of treatment.

$\varepsilon_{max} = (C_0/IC_{50})/[1 + (C_0/IC_{50})]$, was calculated (Table 2). The corresponding average virion and drug half-lives (\pm SD) were 4.6 ± 3.4 hours and 23.0 ± 10.4 hours, respectively, consistent with previously published values.^{1,4} Virion production was blocked by PEG-IFN alfa-2b with an average maximum effectiveness (ε_{max}) of 96%. In Table 2, we also show the estimated drug efficacy 7 days after the first dose, that is, $\varepsilon_{min} = (C_0/IC_{50})(e^{-7k_e})/[1 + (C_0/IC_{50})(e^{-7k_e})]$, just before the second weekly PEG-IFN dose. In 3 of the 4 patients studied, this residual effectiveness is very low ($< 10\%$). In P4, the effectiveness even one week post-injection is 63% and, as Figure 3 illustrates, P4 was the only patient who did not show an increase in viral load during the week. It is noteworthy that this patient was infected with genotype-2 HCV, for which a higher effectiveness of normal IFN alfa has been reported.⁵

Modeling of Pharmacokinetics— Absorption and Elimination Model

The “elimination-only model” used above, while simple, does not adequately describe the absorption of drug from the site of subcutaneous injection into the blood and liver. Thus we also conducted analyses with a model that includes both absorption and elimination of PEG-IFN alfa-2b in the blood.⁹

This “absorption and elimination model” describes the change in the amount of drug in the blood (A) as follows:

$$\frac{dA}{dt} = k_a X - k_e A, \quad (5)$$

where X is the amount of drug at the absorption site, k_a is the rate of absorption, and k_e is the rate of elimination. X can be further characterized as $X = FD e^{-k_a t}$, where F is the bioavailability (the extent to which the active drug enters systemic circulation) and D is the drug dose. The solution to Equation 5 gives an expression for the amount of drug in the blood over time, $A(t)$, and by dividing this expression by the volume of distribution, V_d , we obtain the following equation for the concentration of drug in the blood:

$$C(t) = \frac{k_a FD}{(k_e - k_a) V_d} (e^{-k_a t} - e^{-k_e t}), \quad (6)$$

following a single injection at time $t = 0$. More complex expressions are needed when the drug is given multiple times. Again, changes in drug concentration affect effectiveness; however, to incorporate the effects of a delay between PEG-IFN alfa-2b binding its receptor and beginning its biological action, we assume that the effectiveness at time t depends on the drug concentration at time $t - \tau$, that is, there is a delay of length τ between a

cell sensing an IFN concentration $C(t)$ and responding to it. Thus, for $t > \tau$,

$$\varepsilon(t) = \frac{C(t - \tau)}{IC_{50} + C(t - \tau)}. \quad (7)$$

Simulated changes in concentration and effectiveness with this model, as described by Equations 6 and 7, are displayed in Figure 2. The absorption and elimination model (Equations 1, 6, and 7) was also fitted to data over the first 7 days of therapy and gave fits comparable to those shown in Figure 3 (data not shown). Conceptually, this model has an advantage over the elimination-only model in that it fully separates pharmacokinetic effects from the delays intrinsic to the interferon response. However, it is more complicated mathematically, has an additional parameter, and requires software specially designed to analyze delay-differential equations.

SUMMARY

Administration of PEG-IFN alfa-2b plus ribavirin results in early HCV RNA decays in HIV-HCV co-infected patients, followed by viral load increases as the drug concentration and efficacy decline between doses. When the next dose is administered 1 week later, the same pattern is observed. We have used two pharmacokinetic models—one that includes drug elimination only and one that considers both absorption and elimination—to describe changes in concentration and drug effectiveness in blocking virion production during early therapy with PEG-IFN alfa-2b (12 kDa). We have incorporated each of these pharmacokinetic models into the Neumann et al⁴ model of viral dynamics to describe the effect that changes in drug concentration and effectiveness can have on HCV RNA. In this initial modeling study we did not consider the pharmacokinetics of ribavirin because the drug is administered twice daily. Analyzing data from 4 patients, we obtained good agreement between the models and the measured viral load data, were able to account for the observed increases in HCV RNA, and generated estimates of drug effectiveness in blocking virion production. In contrast to our previous work,⁴ we found that effectiveness is not a constant but changes with time, having a maximum and then decaying until the subsequent dose. Our results suggest that without the modifications suggested here, the Neumann et al⁴ model—with its assumption of fixed drug effectiveness—is not appropriate for the analysis of treatment data obtained with PEG-IFN alfa-2b. As these preliminary findings are based on data from only 4 patients, subsequent analyses in larger patient cohorts are warranted to further our understanding of the pharmacokinetics and viral dynamics in patients receiving PEG-IFN alfa-2b.

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ABBREVIATIONS

HCV hepatitis C virus
 HIV human immunodeficiency virus
 PEG-IFN pegylated interferon alfa-2b

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