

COMMENTARY

A Model-Based Illustrative Exploratory Approach to Optimize the Dosing of Peg-IFN/RBV in Cirrhotic Hepatitis C Patients Treated With Triple Therapy

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Hézode *et al.* recently reported the frequent occurrence of anemia and thrombocytopenia in the ANRS-CO20-CUPIC cohort of hepatitis C virus (HCV) cirrhotic experienced patients treated with pegylated-interferon (Peg-IFN), ribavirin (RBV), and telaprevir or boceprevir.^{1,2} Using frequent measurements of serum drug concentrations, hemoglobin, and platelet concentrations obtained in 15 patients of this cohort, we show how an on-treatment model-based approach could be used to individualize dose regimen and avoid the occurrence of RBV-induced anemia and Peg-IFN-induced thrombocytopenia.

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In this commentary, we provide results from 15 HCV genotype 1 patients included in the MODCUPIC study, nine receiving telaprevir and six boceprevir. Twelve (80%) were men, with a median (min-max) age of 55 (44–64) years. Eleven patients received Peg-IFN- α 2a (eight in telaprevir group, three in boceprevir group), three patients Peg-IFN- α 2b (all in boceprevir group), and one patient in the telaprevir group did not receive any injection of Peg-IFN. The observed drug concentrations, the estimated steady-state trough serum concentrations, C_{ss} , and effectiveness EC_{50} for all drugs are available in Laouéan *et al.*³ Five patients received erythropoietin in supplementation (two in the telaprevir group, three in the boceprevir group) and hemoglobin level and platelet counts were censored afterwards.

RBV-induced anemia modeling

The median (min-max) baseline hemoglobin level was 15.1 g/dl (10.8–16.0) (15.4 g/dl (10.8–16.0) in the telaprevir group and 14.5 g/dl (12.6–15.8) in the boceprevir group, $P = 0.3$). The hemoglobin level decreased over time in all patients (**Supplementary Figures S1 and S2, online**) and was well captured by our model (**Supplementary Figure S3**). Adding the other drugs, Peg-IFN and protease inhibitors (PIs) did not improve the fit of the data (not shown). There was no significant effect of gender on model parameters. The model predicted that the concentration leading to a 50% blocking effectiveness of RBV in blocking hemoglobin production, IC_{50}^{RBV} , was equal to 7,090 ng/ml (**Supplementary Table S1**), leading to a median predicted hemoglobin level at steady state, Hb_{ss} , of 10.0 g/dl (7.8–11.8)

(10.6 g/dl (7.8–11.6) in the telaprevir group and 9.1 g/dl (8.0–11.8) in the boceprevir group, $P = 0.5$). This corresponds to a median predicted change in hemoglobin level of 4.4 g/dl (2.1–6.6) (4.2 g/dl (2.1–5.5) in the telaprevir group and 4.9 g/dl (3.3–6.6) in the boceprevir group, $P = 0.4$). **Figure 1a** shows the relationship between individual predicted RBV concentration at steady state (C_{ss}^{RBV}) and effect (blocking production of hemoglobin). For the six patients (40%) who had $Hb_{ss} < 10$ g/dl (**Table 1**), the model predicted that a median RBV dose reduction of 373 mg/day (45–670) would be needed to avoid anemia corresponding to a median dose reduction of 31% (4–67).

Peg-IFN-induced thrombocytopenia modeling

Median baseline platelet counts were 125,500/mm³ (39,000–230,000) (126,000/mm³ (67,000–230,000) in Peg-IFN- α 2a patients and 80,000/mm³ (39,000–161,000) in Peg-IFN- α 2b patients, $P = 0.4$). The platelet counts decreased over time in all patients (**Supplementary Figures S4 and S5**) and could be well captured by our model (**Supplementary Figure S6**). Adding the other drugs (RBV and PIs) did not improve the fit of the data. The model predicted that the concentration leading to a 50% blocking effectiveness of Peg-IFN in blocking platelets production, $IC_{50}^{Peg-IFN}$, was equal to 104 ng/ml (**Supplementary Table S1**), leading to a median predicted platelet counts at steady state, PLT_{ss} , of 66,720/mm³ (31,400–121,900) (67,270/mm³ (39,370–121,900) in Peg-IFN- α 2a patients and 60,000/mm³ (31,400–108,300) in Peg-IFN- α 2b patients, $P = 0.7$), corresponding to a median predicted change in platelet counts of 51,490/mm³ (16,670–

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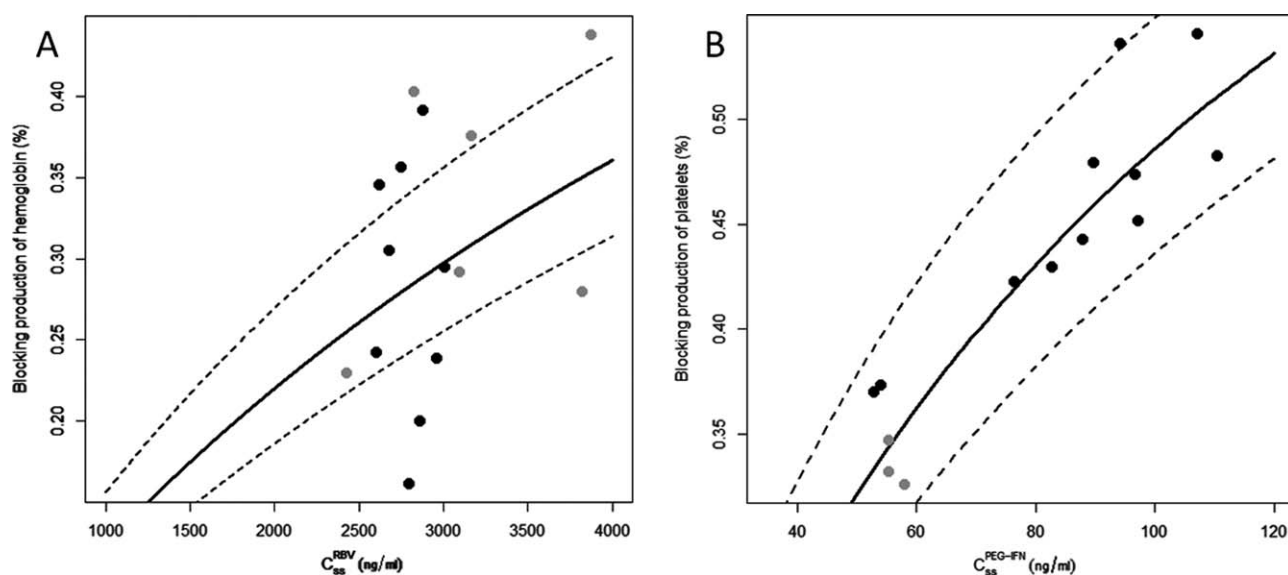


Figure 1 Relationship between: (a) RBV predicted trough serum concentration at steady state (C_{ss}^{RBV}) and predicted blocking production of hemoglobin ($\frac{C_{ss}^{RBV}}{C_{ss}^{RBV} + IC_{50}^{RBV}}$) and (b) Peg-IFN predicted trough concentration at steady state ($C_{ss}^{Peg-IFN}$) and predicted blocking production of platelets ($\frac{C_{ss}^{Peg-IFN}}{C_{ss}^{Peg-IFN} + IC_{50}^{Peg-IFN}}$). Nine patients in the telaprevir group in **a** (black) and six patients in the boceprevir group (gray). Eleven patients in the Peg-IFN- α 2a group in **b** (black) and three patients in the Peg-IFN- α 2b group (gray). The lines denote the predictions with the mean blocking production and the dotted lines denote 95% confidence interval computed with the standard errors predicted by the Fisher Information Matrix.

Table 1 Individual parameter estimates of the RBV-induced anemia model (Hb_0 , C_{ss}^{RBV} , and Hb_{ss}) and proposed RBV dosage modifications for $Hb_{ss} \geq 10$ g/dl and the Peg-IFN-induced thrombocytopenia model (PLT_0 , $C_{ss}^{Peg-IFN}$, and PLT_{ss}) and proposed Peg-IFN dosage modifications for $PLT_{ss} \geq 50,000/mm^3$

Patient	Treatment group PI	Treatment group Peg-IFN	RBV bid dose (mg/day)	Hb_0 (g/dl)	C_{ss}^{RBV} (ng/ml)	Hb_{ss} (g/dl)	Adjusted RBV dose for targeting		Peg-IFN dose (μ g/week)	PLT_0 (/mm ³)	$C_{ss}^{Peg-IFN}$ (ng/ml)	PLT_{ss} (/mm ³)	Adjusted Peg-IFN dose for targeting
							$Hb_{ss} \geq 10$ g/dl (mg/day)	$PLT_{ss} \geq 50,000/mm^3$ (μ g/week)					
1	Boceprevir	2b	1,000	15.5	2,827	9.2	807	100	162,060	55.3	108,301	—	
2	Boceprevir	2a	1,200	15.1	3,874	8.4	781	180	193,480	52.8	121,874	—	
3	Boceprevir	2a	1,200	14.4	3,162	9.0	874	180	105,610	54.0	66,173	—	
4	Boceprevir	2b	1,000	11.4	3,092	8.0	330	100	48,073*	55.4	31,402	—	
5	Boceprevir	2b	1,200	15.4	2,428	11.8	—	100	88,981	57.9	59,999	—	
6	Boceprevir	2a	1,000	15.8	3,820	11.4	—	180	228,620	96.7	120,264	—	
7	Telaprevir	2a	1,000	12.8	2,875	7.8	439	135	123,540	107.1	56,680	—	
8	Telaprevir	2a	1,200	15.3	2,746	9.9	1,154	180	130,520	89.6	67,922	—	
9	Telaprevir	2a	1,000	14.2	2,602	10.7	—	180	76,232	82.6	43,486	125	
10	Telaprevir	2a	1,200	15.3	2,678	10.6	—	180	116,480	76.4	67,267	—	
11	Telaprevir	2a	1,000	14.2	3,008	10.0	—	180	165,530	110.4	85,613	—	
12	Telaprevir	2a	1,000	13.1	2,793	11.0	—	180	134,960	97.2	74,015	—	
13	Telaprevir	2a	1,200	15.2	2,958	11.6	—	180	72,758	87.8	40,545	103	
14	Telaprevir	—	1,200	13.22	2,860	10.6	—	—	—	—	—	—	
15	Telaprevir	2a	1,000	15.4	2,621	10.1	—	180	84,863	94.2	39,365	109	

Hb_0 , baseline hemoglobin level; PLT_0 , baseline platelet counts; C_{ss}^{RBV} , steady state trough ribavirin (RBV) plasma concentrations; $C_{ss}^{Peg-IFN}$, steady state trough pegylated interferon (Peg-IFN) plasma concentrations; Hb_{ss} , hemoglobin level at steady state (in bold if <10 g/dl); PLT_{ss} , platelets count at steady state (in bold if <50,000/mm³).

*One patient had a baseline platelet count <50,000/mm³.

108,400) (60,940/mm³ (32,210–108,400) in the Peg-IFN- α 2a group and 28,980/mm³ (16,670–53,760) in the Peg-IFN- α 2b group, $P = 0.09$). **Figure 1b** shows the relationship between individual Peg-IFN concentration ($C_{ss}^{Peg-IFN}$) and effect (blocking production of platelets). Four patients

out of 14 (29%) had predicted $PLT_{ss} < 50,000/mm^3$ using the current dose or Peg-IFN, but one patient had a baseline PLT below 50,000/mm³ (**Table 1**). For these three patients the model predicted that a median Peg-IFN dose reduction of 37 μ g/week (25–37) would be needed to avoid

thrombocytopenia, corresponding to a median dose reduction of 60% (57–70).

Towards an approach integrating efficacy and toxicity

The increasing availability of highly effective treatment holds the promise that high rates of sustained virological response (SVR) with lower toxicity can be reached. However, the CUPIC study reporting an incidence of 34.1% and 17.0% for grade 2–4 anemia and grade 3–4 thrombocytopenia, respectively,^{1,2} should serve as a reminder that safety may remain an important concern in HCV treatment management, in particular in patients with advanced liver disease whose prevalence in real life is larger than in clinical trials.

Using a model to relate anemia and thrombocytopenia to RBV and Peg-IFN exposure, respectively, we predicted that a dose reduction of RBV and Peg-IFN in 40% and 30% of patients, respectively, would have been needed to avoid toxicity. This would correspond to a median dose reduction of 31% and 60% for RBV and Peg-IFN, respectively. These adjusted RBV and Peg-IFN doses are not practical to administer in actual clinical practice. But here we explore the feasibility and provide an order of magnitude of the amplitude of dose reduction to avoid the occurrence of toxicity.

Because both RBV and Peg-IFN have modest effectiveness against HCV, at least in the first weeks of treatment, where most viruses are sensitive to PIs,³ this dose reduction is unlikely to have a significant impact on the early viral kinetics. Consistent with this prediction, Poorad *et al.* showed in a randomized clinical trial that reduction in RBV dosage (up to 50% of the initial amount) throughout the course of triple therapy did not affect SVR rates.⁴

Clearly, the small sample size of our population is the main limitation of the study. The lack of statistical power may explain the lack of any significant effect of PI exposure on hemoglobin level and platelet count kinetics.^{5,6} It is well known that RBV causes mainly dose-dependent hemolytic anemia, leading to a reduction in the hemoglobin level,⁷ whereas Peg-IFN induces mainly suppression of hematopoiesis, leading to a reduction in platelet counts.⁸ This small population also constrained us to analyze the effects of RBV and Peg-IFN separately and independently and we could not evaluate the effect association between the two effects, such as the fact that the bone marrow suppressive effect of Peg-IFN may also contribute to the associated anemia.⁹

Both RBV and Peg-IFN concentrations were close to an inhibition effect in hemoglobin level and platelet counts, respectively, equal to 50%. Interestingly, we previously reported that Peg-IFN concentrations in this population also led to an antiviral effect in blocking viral production close to 50%.³ The fact that Peg-IFN concentrations led to comparable levels of efficacy and toxicity suggests that Peg-IFN has a particularly narrow therapeutic index and reinforces the interest of Peg-IFN therapeutic monitoring in this population. Of note, it should be acknowledged that the effects of RBV and Peg-IFN were described by turnover indirect models with a maximum inhibition of 100% and more data will be needed to evaluate this assumption.

In conclusion, by showing that the serum PK of RBV and Peg-IFN can be used to characterize the kinetics of hemo-

globin level and platelet counts, respectively, this study suggests that individual monitoring of the drug concentrations may improve the management of anti-HCV therapy. This approach, combined with a viral kinetic model that can tease out the effect of each drug on the virologic response,³ holds the promise that integrated model-based approaches could optimize the trade-off between the efficacy and safety of triple therapy. However, this approach will need to be validated on large populations.

Patients and data

MODCUPIC is a substudy of the French ANRS-CO20-CUPIC cohort.³ From September 2011 to September 2012, patients chronically monoinfected with HCV genotype 1, compensated cirrhosis, nonresponders to a prior IFN-based therapy, and who started triple therapy were recruited. Telaprevir-based therapy included 12 weeks of telaprevir (750 mg tid) with Peg-IFN- α 2a (180 μ g/week) and RBV (1,000 or 1,200 mg/day, depending on body weight), then 36 weeks of Peg-IFN- α 2a/RBV. Boceprevir-based therapy included 4 weeks (lead-in phase) of Peg-IFN- α 2b (1.5 μ g/kg/week) or Peg-IFN- α 2a (180 μ g/week) and RBV (800 or 1,400 mg/day, depending on body weight), then 44 weeks of Peg-IFN- α 2b/RBV and boceprevir (800 mg tid).

Written informed consent was obtained before enrollment. The protocol was approved by the Ile-de-France IX Ethics Committee (Créteil, France).

Blood samples were collected post-PIs initiation at hours 0, 8, days 0, 1, 2, 3, and weeks 1, 2, 3, 4, 8, and 12. There were two additional visits during the boceprevir lead-in phase. Details of bioanalytical methods are available in Laouénan *et al.*³

Pharmacokinetic and pharmacodynamic model

We assumed that the changes in hemoglobin level and platelet counts were mainly driven by RBV and Peg-IFN concentrations, respectively.¹⁰ The effects of RBV and Peg-IFN were described by turnover indirect models assuming a maximum inhibition of 100% given by:

$$\frac{dHb}{dt} = Hb_0 \times k_{out}^{Hb} \times \left(1 - \frac{C^{RBV}(t)}{C^{RBV}(t) + IC_{50}^{RBV}} \right) - k_{out}^{Hb} \times Hb(t)$$

$$\frac{dPLT}{dt} = PLT_0 \times k_{out}^{PLT} \times \left(1 - \frac{C^{Peg-IFN}(t)}{C^{Peg-IFN}(t) + IC_{50}^{Peg-IFN}} \right) - k_{out}^{PLT} \times PLT(t)$$

where Hb_0 (PLT_0) is the baseline level of hemoglobin (platelet counts), k_{out}^{Hb} (k_{out}^{PLT}) is the rate constant of hemoglobin (platelets) elimination, safety IC_{50}^{RBV} ($IC_{50}^{Peg-IFN}$) is the half maximal effective RBV (Peg-IFN) concentration, and $C^{RBV}(t)$ ($C^{Peg-IFN}(t)$) is the trough concentration predicted by a PK model previously developed.³ In brief, $C^{RBV}(t)$ and $C^{Peg-IFN}(t)$ were fitted using an exponential model to obtain the trough concentration at steady state C_{ss}^{RBV} and $C_{ss}^{Peg-IFN}$. We assumed a linear PK for both drugs.

Data analysis and parameter estimation

Wilcoxon tests were used to compare baseline hemoglobin level (boceprevir vs. telaprevir) and baseline platelet counts (Peg-IFN- α 2a vs. -2b). Parameters (Hb_0 , PLT_0 , k_{out}^{Hb} , k_{out}^{PLT} , $IC_{50}^{Peg-IFN}$, IC_{50}^{RBV}) were estimated using longitudinal data

analyzed by nonlinear mixed-effect models with the Stochastic Approximation Expectation Minimization (SAEM) algorithm in MONOLIX v. 4.2 (<http://www.lixoft.eu>), assuming exponential random effects models and additive error models. The model codes and example datasets are provided in the Supplementary Materials online. Model evaluation was performed using goodness-of-fit plots, as well as the individual weighted residuals (IWRES) and the normalized prediction distribution errors (NPDE) over time. Wald tests on Hb_0 and IC_{50}^{RBV} were used to assess the influence of gender for RBV-induced anemia. We also tested using the Bayesian information criteria whether the addition of other drug had an effect in each model.

Prediction of individual dosage regimen avoiding toxicity

Maximum *a posteriori* was used to obtain individual Empirical Bayesian Estimates (EBE). For each patient, from the EBEs, hemoglobin level and platelet counts at steady state, Hb_{ss} and PLT_{ss} , was obtained as:

$$Hb_{ss} = Hb_0 \times \left(1 - \frac{C_{ss}^{RBV}}{C_{ss}^{RBV} + IC_{50}^{RBV}} \right)$$

$$PLT_{ss} = PLT_0 \times \left(1 - \frac{C_{ss}^{Peg-IFN}}{C_{ss}^{Peg-IFN} + IC_{50}^{Peg-IFN}} \right)$$

where $\frac{C_{ss}^{RBV}}{C_{ss}^{RBV} + IC_{50}^{RBV}}$ and $\frac{C_{ss}^{Peg-IFN}}{C_{ss}^{Peg-IFN} + IC_{50}^{Peg-IFN}}$ represent the blocking production of hemoglobin and platelets, respectively. Wilcoxon tests were used to compare Hb_{ss} and PLT_{ss} between treatment groups. If Hb_{ss} was predicted below 10 g/dl, the maximum dose of RBV leading to $Hb_{ss} \geq 10$ g/dl was calculated. If PLT_{ss} was predicted below 50,000/mm³, the maximum dose of Peg-IFN leading to $PLT_{ss} \geq 50,000$ /mm³ was calculated.

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