

Using pharmacokinetic and viral kinetic modeling to estimate the antiviral effectiveness of telaprevir, boceprevir and Peg-IFN during triple therapy in treatment-experienced HCV infected cirrhotic patients

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CONTEXT

- Triple therapy (HCV genotype 1)
 - Bitherapy (PEG-IFN/RBV) + 1 Protease Inhibitor (PI)
 - PI: **telaprevir (TVR)** or **boceprevir (BOC)**
- Mathematical modeling of viral kinetic after treatment initiation has brought critical insights for the understanding of the virus pathogenesis, the drug's mechanism of action and its antiviral effectiveness [1]
- The efficacy of triple therapy remains suboptimal in cirrhotic experienced-patients

OBJECTIVE

- To better understand the origin of this impaired response by estimating the antiviral effectiveness of each drug in real life setting

METHODS

Data = MODCUPIC - ANRS trial (Pr Marcellin, Paris, France)

- Ancillary study of CUPIC ANRS-CO20 (Dr Hézode, Paris, France)
- Multicentric cohort of patients with HCV genotype 1 monoinfected
- Compensated cirrhosis (F4) who failed prior treatment by bitherapy
- Patients were prospectively included to receive without randomization either:
 - **TVR + PEG-IFN/RBV** or **BOC + PEG-IFN/RBV**
- Patients in BOC group received PEG-IFN/RBV during the first 4 weeks lead-in phase
- Frequent Viral Load (VL) and drug concentration measurements within 12 weeks after PI initiation

Drug pharmacokinetic (PK) modeling:

- For Peg-IFN and RBV: the trough serum concentrations, noted $C^{Peg-IFN}(t)$ and $C^{RBV}(t)$, respectively were fitted using an exponential model:

$$C^{Peg-IFN}(t) = C_{ss}^{Peg-IFN} \times (1 - e^{-kt})$$

$$C^{RBV}(t) = C_{ss}^{RBV} \times (1 - e^{-kt})$$

where C_{ss} is the trough concentration at steady state and k the rate constant of elimination

- For Pis: $C^{PI}(t)$ were fitted using constant model:

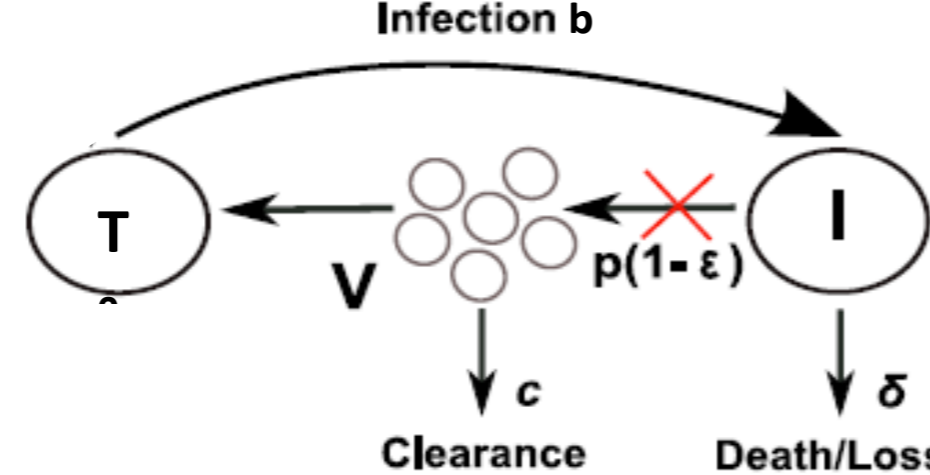
$$C^{PI}(t) = C_{ss}^{PI}$$

Viral kinetic (VK) modeling: standard viral biphasic model [2]

Ordinary Differential Equations (ODE):

$$\begin{cases} \frac{dI}{dt} = bVT_0 - \delta I \\ \frac{dV}{dt} = (1-\epsilon)pI - cV \end{cases}$$

Figure 1. Viral kinetic model



Where I : the infected cells, V : the VL, T_0 : the target cell number (which is assumed to be constant and equal to its pretreatment value), b : the rate at which target cells are infected (fixed to 10^{-6} IU/mL/day), p : the viral production rate per infected cell in absence of treatment (fixed to 10 IU/L/cell/day), V_0 : the baseline VL, c : the clearance rate of VL, δ : the loss rate of infected cells, ϵ : the drug efficacy (treatment is assumed to reduce the average rate of viral production per cell from p to $p(1-\epsilon)$)

- The effectiveness of each drug in blocking viral production was described by an E_{max} model assuming a maximum inhibition of 100%:

$$\epsilon^{PI}(t) = \frac{C^{PI}(t)}{C^{PI}(t) + EC_{50}^{PI}}$$

$$\epsilon^{Peg-IFN}(t) = \frac{C^{Peg-IFN}(t)}{C^{Peg-IFN}(t) + EC_{50}^{Peg-IFN}}$$

Where EC_{50} is the drug concentration at which the drug is 50% effective

- **PK/VK model**: the combined effect of PIs and Peg-IFN was modeled using a Bliss independent action model and the total efficacy $\epsilon(t)$ was given by:

$$(1 - \epsilon(t)) = (1 - \epsilon^{PI}(t))(1 - \epsilon^{Peg-IFN}(t))$$

- Since the effect of RBV on the early virological response is expected to be modest we did not incorporate the effect of RBV into the reference model

Parameter estimation

- Parameters were estimated using Nonlinear mixed effect models (NLMEM) with SAEM algorithm in MONOLIX [3] taking into account Below Limit of Detection data[4]
- Wald test was performed to detect a difference between treatment groups for each parameters of the PK/VK model (V_0 , c , δ and EC_{50}^{PI} and $EC_{50}^{Peg-IFN}$)
- Permutation test ($n=1000$ permutations) was performed if Wald test was significant for a difference of treatment efficacy as an inflation of type I error of Wald test was expected [5] to obtained the distribution of the p-values under the null hypothesis of no treatment effect
- Individual Empirical Bayesian Estimates parameters were obtained by computing for each patient the Maximum A Posteriori estimate. The individual antiviral effectiveness at steady state, ϵ_{ss} , of each agent was defined by:

$$\epsilon_{ss}^{PI} = \frac{C_{ss}^{PI}}{C_{ss}^{PI} + EC_{50}^{PI}}$$

$$\epsilon_{ss}^{Peg-IFN} = \frac{C_{ss}^{Peg-IFN}}{C_{ss}^{Peg-IFN} + EC_{50}^{Peg-IFN}}$$

[1] Guedj, Rong, Dahari, Perelson. J Viral Hepat 2010, 17(12):825-833.

[2] Neumann, Lam, Dahari, Gretch, Wiley, Layden, Perelson. Science 1998, 282:103-7.

[3] <http://lixsoft.eu>

[4] Samson, Lavielle, Mentré. Comput Statist Data Anal 2006, 51:1562-1574.

[5] Laouénan, Guedj, Mentré. BMC Med Res Methodol 2013, 13:60.

[6] Chatterjee, Guedj, Perelson. Antivir Ther 2012;17:1171-1182.

RESULTS

- Fifteen patients were included (9 TVR, 6 BOC)
- Median [min-max] age: 54.6 years [43.9-58.9]; males: 13 (87%)

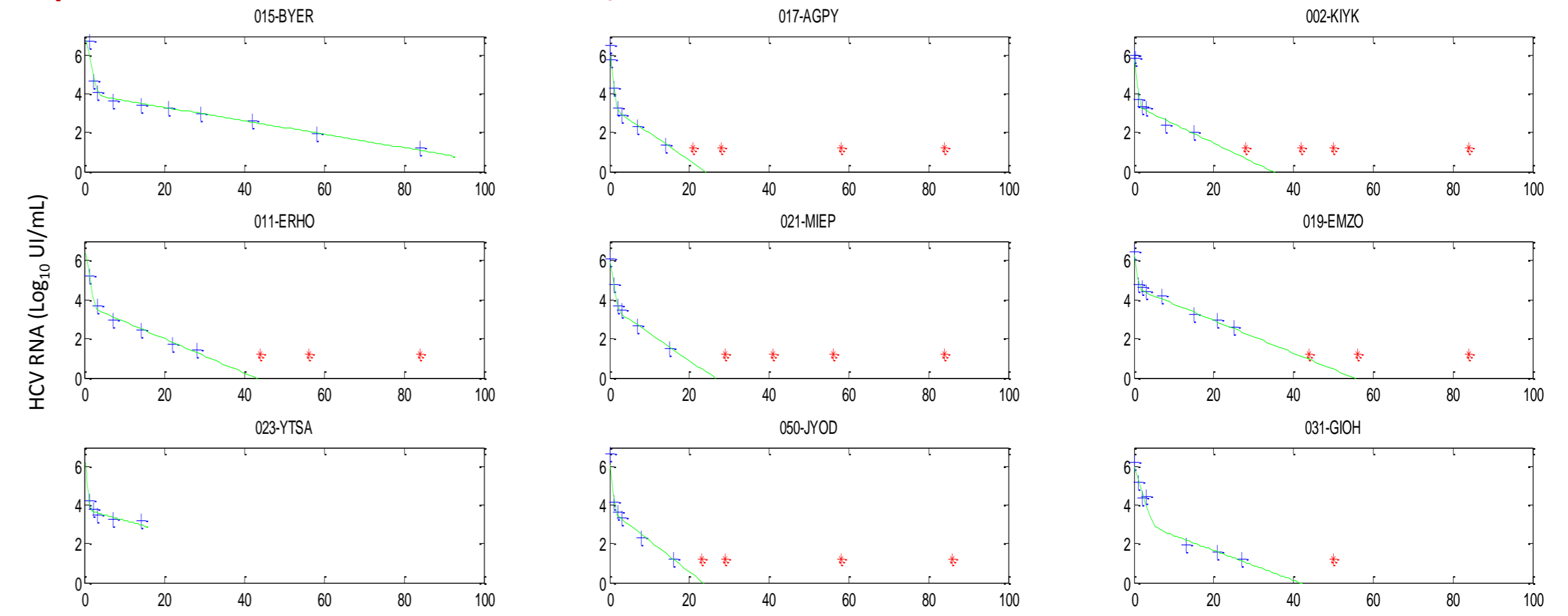
Table 1. Individual predicted trough concentrations at steady state (C_{ss})

	n	median [min; max]
$C_{ss}^{telaprevir}$ ($\mu\text{mol/l}$)	9	3.77 [2.68; 5.98]
$C_{ss}^{boceprevir}$ ($\mu\text{mol/l}$)	6	3.92 [3.22; 7.64]
$C_{ss}^{Peg-IFN-\alpha 2a}$ (ng/ml)	11	89.6 [52.8; 110.4]
$C_{ss}^{Peg-IFN-\alpha 2b}$ (ng/ml)	3	55.4 [55.3; 57.9]
C_{ss}^{RBV} (ng/ml)	15	2,860 [2,428; 3,874]
$C_{ss}^{telaprevir}$ ($\mu\text{mol/l}$)	9	3.77 [2.68; 5.98]

- The PK/VK model can well describe the viral kinetics in all patients (Figure 2) and model parameters were estimated with good precision (Table 2)

Figure 2. Individual fits of 15 patients included

9 patients treated with: TVR + PEG-IFN/RBV



6 patients treated with: BOC + PEG-IFN/RBV

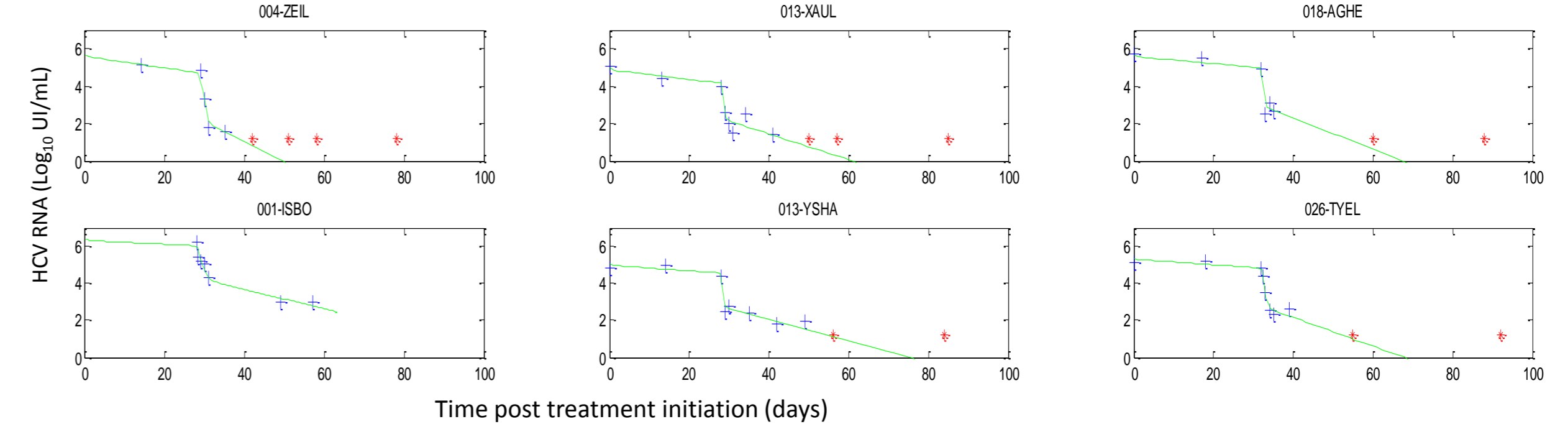


Table 2. Parameter estimates with relative standard errors (RSE)

Parameter (units)	Estimate	RSE (%)
V_0^{TVR} (\log_{10} IU/mL)	6.43	2
V_0^{BOC} (\log_{10} IU/mL)	5.52	3
c (day^{-1})	3.98	12
δ (day^{-1})	0.18	11
$EC_{50}^{PEG-IFN}$ (ng/ml)	106	40
EC_{50}^{TVR} ($\mu\text{mol/l}$)	0.009	30
EC_{50}^{BOC} ($\mu\text{mol/l}$)	0.04	43
ω_{V_0}	0.07	20
ω_c	0.47	19
ω_δ	0.42	16
$\omega_{EC_{50}^{PEG-IFN}}$	0.67	30
$\omega_{EC_{50}^{PI}}$	0.61	32
σ	0.27	7

- Both PIs achieved similar level of molar concentrations ($P=0.5$) (Table 1), but there was a significant difference of EC_{50} ($P = 0.008$) (Table 2), leading to a larger ϵ_{ss} than boceprevir ($\epsilon_{ss}^{TVR} = 99.8\%$ vs $\epsilon_{ss}^{BOC} = 99.0\%$, $P = 0.002$)

- In all patients $\epsilon_{ss}^{Peg-IFN}$ was modest (43.4%) and there was no significant contribution of RBV exposure on the total antiviral effectiveness. The second phase of viral decline was slow ($\delta = 0.19 \text{ day}^{-1}$)

CONCLUSIONS

- Small sample size non randomized study
- First characterization of the relationship between drug concentrations involved in triple therapy and early HCV viral kinetics treated with TVR or BOC
- This PK/VK model provides important insights into the understanding of the impaired response to triple therapy in hard-to treat patients
- ϵ_{ss}^{TVR} was comparable to previously published in non-cirrhotic naive patients [1] and ϵ_{ss}^{BOC} was significantly lower than ϵ_{ss}^{TVR} (even adjusted on V_0)
- Biphasic viral decline was slower than what had been observed in non-cirrhotic naive patients during TVR monotherapy and was close to typical values observed during PEG-IFN/RBV therapy [6]
- The suboptimal antiviral effectiveness of Peg-IFN/RBV and the low loss of infected cells (three times smaller than in non-cirrhotic naive patients treated with TVR monotherapy) suggest that longer treatment duration might be needed in cirrhotic treatment experienced-patients and that future IFN-free regimen may be particularly beneficial to these patients