Research Article

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# HCV kinetic and modeling analyses indicate similar time to cure among sofosbuvir combination regimens with daclatasvir, simeprevir or ledipasvir

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**Background & Aims**: Recent clinical trials of direct-acting-antiviral agents (DAAs) against hepatitis C virus (HCV) achieved >90% sustained virological response (SVR) rates, suggesting that cure often took place before the end of treatment (EOT). We sought to evaluate retrospectively whether early response kinetics can provide the basis to individualize therapy to achieve optimal results while reducing duration and cost.

**Methods**: 58 chronic HCV patients were treated with 12-week sofosbuvir + simeprevir (n = 19), sofosbuvir + daclatasvir (n = 19), or sofosbuvir + ledipasvir in three French referral centers. HCV was measured at baseline, day 2, every other week, EOT and 12 weeks post EOT. Mathematical modeling was used to predict the time to cure, i.e., <1 virus copy in the entire extracellular body fluid.

**Results**: All but one patient who relapsed achieved SVR. Mean age was 60 ± 11 years, 53% were male, 86% HCV genotype-1, 9% HIV coinfected, 43% advanced fibrosis (F3), and 57% had cirrhosis. At weeks 2, 4 and 6, 48%, 88% and 100% of patients had HCV <15 IU/ml, with 27%, 74% and 91% of observations having target not detected, respectively. Modeling results predicted that 23 (43%), 16 (30%), 7 (13%), 5 (9%) and 3 (5%) subjects were predicted to reach cure within 6, 8, 10, 12 and 13 weeks of therapy, respectively. The modeling suggested that the patient who relapsed would have benefitted from an additional week of sofosbuvir + ledipasvir. Adjusting duration of treatment according to the modeling predicts reduced medication costs of 43–45% and 17–30% in subjects who had HCV <15 IU/ml at weeks 2 and 4, respectively.

**Conclusions**: The use of early viral kinetic analysis has the potential to individualize duration of DAA therapy with a projected average cost saving of 16–20% per 100-treated persons.



Keywords: HCV; Viral kinetics; Mathematical modeling; SVR; Duration of therapy.

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*Abbreviations:* HCV, hepatitis C virus; DAAs, direct-acting antiviral agents; SVR, sustained virological response.

## Introduction

Hepatitis C virus (HCV) is a major cause of chronic liver disease, with an estimated 170 million people infected worldwide [1]. The development and recent approval of direct-acting antiviral agents (DAAs) has led to a revolution in the treatment of HCV with high sustained virological response (SVR) rates and virtual elimination of serious side effects [2]. Sofosbuvir-based regimens, including ledipasvir, simeprevir or daclatasvir achieve SVR rates of over 90% in all patient populations, including difficult to treat patients with cirrhosis, HIV co-infection, and previous non-responders [3–6]. However, high medication costs have limited access to treatment and have placed a substantial financial burden on insurers and national healthcare systems [7,8].

Historically, on-treatment HCV RNA levels served as an indicator of treatment outcome [9]. In particular, during interferon (IFN)-alpha therapy, on-treatment virus levels were a better predictor of treatment failure than of treatment success and thus provided the basis for treatment stopping rules [10]. With the advent of DAAs, the exceptionally high SVR rates achieved have made it far less important to predict response versus non-response and early viral kinetics (i.e. time to viral negativity) do not predict treatment failure [11,12]. However, it would be

extremely useful if early HCV kinetics could be used to determine duration of treatment needed to achieve cure, i.e. SVR.

In a previous study, we reported for the first time the use of real-time mathematical modeling of on-treatment HCV kinetics to individualize duration of IFN-free therapy with intravenous silibinin including the empowerment of the patient to participate in treatment decisions [13]. The application of similar modeling approaches to treatment with DAAs could provide the basis for using early on-treatment HCV RNA levels to predict duration of treatment needed to achieve cure and thus shorten treatment and reduce costs for some patients. Additionally, shorter regimens with low pill burdens, and few adverse effects could improve patient adherence in difficult to treat populations [6].

The objective of this study was to use kinetic analysis and modeling of early on-treatment HCV RNA levels to predict the duration of DAA therapy needed to achieve SVR. The analysis was performed retrospectively on data collected from patients treated with sofosbuvir (SOF) in combination with simeprevir (SIM), daclatasvir (DAC), or ledipasvir (LEDI).

## Patients and methods

### *Patients*

Data were obtained from 60 consecutive patients who received treatment for chronic HCV at three French HCV referral centers (Hôpital Européen - Marseille, Hôpital Saint Joseph-Marseille and Centre Hospitalier - Hyères) between December 2014 and January 2015. Patients were treated with SOF in conjunction with ribavirin (n = 2), SIM (n = 19), DAC (n = 19), or LEDI (n = 20). Due to the small n of the ribavirin treatment arm, these 2 patients were excluded from analysis and modeling in the current study. Patients were treated according to the recommendations of the French association for the study of the liver (AFEF), taking into consideration previous treatment, HCV genotype, fibrosis stage $\geqslant$F3 (performed less than six months before the start of therapy), and/or experts consensus recommendations [14].

All patients agreed to have their samples used for research purposes and the study was performed in compliance with Article L1121-1 of the French Public Health law. The study was approved by the steering committee of each participating hospital.

Fibrosis stage was evaluated by FibroTest [15] or FibroScan [16,17] and classified according to the Metavir scoring system following French Guidelines [18]. Values of FibroTest $\geqslant$0.59 or FibroScan $\geqslant$ 9.5 kPa were defined as advanced fibrosis ($\geqslant$F3) and values of FibroTest $\geqslant$0.79 or FibroScan $\geqslant$12.1 kPa were defined as cirrhosis (F4) [19–21].

### *HCV RNA measurements*

HCV viral loads were assessed using Cobas Taqman HCV Test v2.0 (Roche Diagnostics France; limit of quantification 15 IU/ml) [22]. HCV RNA levels were measured at baseline, day 2, and weeks 2, 4, 6, 8 and 12 during therapy and then 4 weeks and 12 weeks after completion of therapy. In the SOF + LEDI group, HCV RNA levels also were measured at week 1.

### *Mathematical modeling*

HCV viral kinetics under therapy was assumed to follow the standard biphasic model [23]:

$$\begin{aligned} dI/dt &= \beta T_0 V - \delta I \\ dV/dt &= (1-\varepsilon)pI - cV \end{aligned} \quad (1)$$

Where $T_0$ represents the number of target cells (i.e., hepatocytes), $I$, the number of infected cells and $V$, is the viral load in blood. Virus, $V$, infects target cells with rate constant $\beta$, generating productively-infected cells, $I$, which produce new virions at rate $p$ per infected cell. Infected cells are lost at a rate $\delta$ per infected cell and virions are assumed to be cleared from blood at rate $c$ per virion. Similar to previous modeling efforts [13,23], we assume the target cell level remained constant during therapy at pretreatment level $T_0 = c\delta/\beta p$. DAA effect $\varepsilon$ is defined as the therapy effectiveness $0 \leqslant \varepsilon \leqslant 1$ in preventing viral production/secretion. Parameter estimates and their inter-individual variability (IIV) estimates were obtained using a maximum-likelihood method by the stochastic approximation expectation–maximization algorithm [24] implemented in MONOLIX version 4.3.2 (Lixoft, Orsay, France). Further details are given in the Supplementary material.

### *Cure boundaries*

The time to cure, or SVR, was defined as the time to reach less than one hepatitis C virion in the entire extracellular body fluid (blood, interstitial and transcellular) volume approximately 13.5 L [13,25–27]. A value of $7 \times 10^{-5}$ for V (IU/ml) was used as the threshold for cure as the concentration of one virion/13,500 ml = $7 \times 10^{-5}$ IU/ml. A secondary, more speculative analysis was performed in which time to cure was defined as less than one virus and infected hepatocyte in the body [13,25–27] (Supplementary material).

### *Statistical analysis*

Associations between either treatment type and patients characteristics were performed using either $\chi^2$ test or Fisher test for categorical variables or non-parametric Wilcoxon test for continuous variables.

For all analyses, a $p$ value of $\leqslant$0.05 was considered as statistically significant. Data analyses were performed using SAS V9.1 software system (SAS Institute Inc., Cary, NC).

## Results

### *Baseline characteristics, viral kinetics and SVR rates*

Mean age was 60 ± 11 years, 30 (53%) were male, 50 (86%) HCV genotype 1, 8 (14%) non-genotype 1 (genotype 3 (n = 1), genotype 4 (n = 6) and genotype 5 (n = 1)), 5 (9%) HIV coinfected, 25 (43%) had severe fibrosis (F3), and 33 (57%) had cirrhosis (Table 1).

Pretreatment HCV RNA levels were significantly ($p$ = 0.007) different among treatment groups with SOF + SIM (5.70 ± 1.05 log IU/ml), SOF + LEDI (5.99 ± 0.46 log IU/ml) and SOF + DAC (6.45 ± 0.45 log IU/ml). The SOF + SIM group had a trend toward a lower proportion of patients with cirrhosis ($p$ = 0.093). In addition, there were significantly less non-responders (NR) to previous treatment in the SOF + LEDI group (50%) compared to SOF + SIM (96%) and SOF + DAC groups (93%; $p$ = 0.014).

Fifty-seven (98%) patients achieved SVR12 with one relapse in the SOF + LEDI group. During therapy, 3 patients (5%) had viral loads <15 IU/ml (detected or target not detected, TND) at day 2, 25 (43%) had <15 IU/ml at week 2, 23 (40%) at week 4, and 7 (12%) at week 6 (Fig. 1A). Three patients (15%) in the SOF + LEDI group had <15 IU/ml (detected) at week 1. In addition, the mean time to reach, TND, was similar among treatment groups, with 2 patients (3%) achieving TND at day 2, 14 (24%) at week 2, 27 (47%) at week 4, 10 (17%) at week 6, and 5 (9%) at week 8 (Fig. 1B). There was no association ($p$ >0.24) between viral response type (i.e., time to viral load <15 IU/ml or TND) and fibrosis stage (cirrhotic *vs.* non-cirrhotic), or previous viral response (NR, Relapse, naïve) during IFN-based regimens (not shown).

### *Viral kinetic parameter estimation*

Model fitting was not performed in 4 patients whose viral load was already <15 IU/ml or TND at day 2 (n = 3) or day 7 (n = 1). The standard biphasic model (Eq. (1))that includes inter-individual variability (IIV, see Supplementary material) in HCV-infected cell