Published in final edited form as:
J Viral Hepat. 2011 April ; 18(4): e52–e60. doi:10.1111/j.1365-2893.2010.01358.x.

Very early prediction of response to HCV treatment with peg-IFN-alfa-2a and ribavirin in HIV/HCV coinfected patients

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Abstract

The objective of the present study was to find very early viral kinetic markers to predict nonresponse to HCV therapy in a group of HIV/HCV-coinfected patients. Twenty-six patients (15 HCV genotype-1 and 11 genotype-3) were treated with a 48-week regimen of peginterferon-alfa-2a (PEG-IFN) (180 μg/week) and weight based ribavirin (11mg/kg/day). Samples were collected at baseline; 4, 8, 12, 18, 24, 30, 36 and 42 hours; days 2, 3, 4, 7, 8, 15, 22, 29, 43 and 57 then weekly and monthly. Five patients discontinued treatment. Seven patients (27%) achieved a sustained virological response (SVR). Nadir HCV RNA levels were observed 1.6±0.3 days after initiation of therapy, followed by a 0.3- to 12.9-fold viral rebound until the administration of the second dose of PEG-IFN, which were not associated with SVR or HCV genotype. A viral decline <1.19 log for genotype-1 and <0.97 log for genotype-3, 2 days after starting therapy, had a negative predictive value (NPV) of 100% for SVR. The day 2 virologic response had a similar positive predictive value (PPV) for SVR as a rapid virologic response at week 4. In addition, a *second-phase*-viral-decline slope (i.e., measured from day 2 to 29) less than 0.3 log/wk had a NPV=100% for SVR.

CONCLUSIONS—First phase viral decline at day 2 and second-phase-viral-decline slope (<0.3 log/wk) are excellent predictors of nonresponse. Further studies are needed to validate these viral kinetic parameters as early on-treatment prognosticators of nonresponse in patients with HCV and HIV.

Keywords

HCV; HIV; Pegylated Interferon and Viral Kinetics

Introduction

Coinfection with human immunodeficiency virus (HIV) and HCV affects approximately 10 million people worldwide [1] and up to 100,000 persons in Brazil [2]. The prevalence of

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Disclosure Financial Support

Conflict of Interest ESAA has received support for travel to international conferences, honoraria for scientific activities and research support from Roche Brazil.

coinfection is as high as 90% among injection drug users and HIV-infected hemophiliacs [3]. Hepatitis C is considered an opportunistic infection in persons with HIV based on prevalence and high rates of HCV-related morbidity and mortality [4,5]. Progression to cirrhosis and hepatocellular carcinoma occurs more rapidly in HIV/HCV-coinfected patients than in HCV-monoinfected individuals [6,7]. Moreover, sustained virological response (SVR) rates to pegylated-interferon (PEG-IFN) and ribavirin are lower in HIV/HCV coinfected [8-12] than in HCV monoinfected patients [13,14]. Therefore, treatment of chronic HCV infection has become a priority in HIV-coinfected patients.

HCV therapy for 48 weeks was recommended for all HCV genotypes in most guidelines designed for HIV/HCV co-infected patients [15,16]. Efforts have been made to identify early predictors of nonresponse in order to limit side effects and to reduce cost in patients who are unlikely to respond with continued therapy [17-19]. Detailed viral kinetic studies, which allow analysis of viral decline before week 4 [20-25], provide a means to assess the predictive value of on treatment response at early time points.

The objective of the present study was to identify very early viral kinetic markers to predict nonresponse to HCV therapy in HIV/HCV-coinfected patients.

Materials and Methods

Patients

The study was approved by the ethics committee at the University of São Paulo *Hospital das Clínicas* and subjects provided written informed consent to participate. Twenty-six HIV-HCV coinfected patients were included. Subjects were HBsAg negative and had no evidence of other causes of liver disease or comorbid illnesses. All patients had well-controlled HIV infection for at least six months on stable highly active antiretroviral therapy (HAART) or without HAART. Standard indications and contraindications for the use of peginterferon and ribavirin were followed [26]. Baseline data are summarized in Table 1 and are further detailed in a recent publication [27].

Treatment procedure

Patients received peginterferon alfa-2a (180 μg/week) and weight based ribavirin (11 mg/kg/day) for 48 weeks. At the outset of the treatment, patients were hospitalized for 48 hours in order to facilitate blood sample collection. After discharge, they were monitored as outpatients. To standardize the treatment regimen, each dose of peginterferon was given on a Monday morning at 08:00. For the initial 4 weeks of treatment, patients took peginterferon under direct observation. At each visit, ribavirin was dispensed in a quantity sufficient to last until the subsequent visit. Each patient received oral instructions and a written schedule for medication and sample collection.

Viral Load Monitoring

Blood samples were collected at the following time points: at baseline; at 4, 8, 12, 18, 24, 30, 36 and 42 hours; on days 2, 3, 4, 7, 8, 15, 22, 29, 43, 57 and 84. . The end-of-treatment response and SVR were evaluated at weeks 48 and 72, respectively. Rapid virologic response (RVR) was defined as HCV RNA <10 IU/ml at day 29 of therapy, complete early virologic response (cEVR) was defined as undetectable HCV-RNA (<10 IU/ml) at week 12, and partial EVR (pEVR) as HCV RNA load decreased ≥2 $\log_{10}$, but detectable at week 12. Based on patient and physician discretion, continued therapy was permitted at week 12 in the absence of cEVR.

Specimens collected for viral quantification were prepared immediately, and the aliquots were frozen at −80°C until processing. The COBAS TaqMan HCV test (Roche Molecular Systems Inc., Branchburg, NJ), with a detection range of 10 to 10,000,000 HCV IU/mL was used for HCV quantification until week 12. The Amplicor HCV test (version 2.0; Roche Diagnostics Corp., Indianapolis, IN) was used for qualitative detection of HCV (limit of detection of 50 HCV IU/ml) at the end of therapy (EOT) (week 48) and follow up at week 72, and genotyping was performed with VERSANT HCV genotype assay (LiPA; Bayer Corp., Tarrytown, NY). The COBAS Amplicor HIV-1 Monitor test (version 1.5; Roche Molecular Systems Inc.), with a detection range of 50 to 100,000 HIV copies/mL, was used for quantification of HIV. All virologic assays were performed at TriCore Reference Laboratories (Albuquerque, NM). The remaining tests were performed in the Hepatitis Laboratory (LIM 47) of the *Hospital das Clínicas*.

Statistical Analysis

We used nonparametric methods in intention-to-treat (ITT) and per protocol (PP) analyses to compare baseline characteristics and viral response parameters of SVR vs. non SVR cases. To compare categorical variables, we used the two-tailed Fisher exact test. Multiple unrelated groups were compared using the Kruskal Wallis test (e.g., see viral decline patterns in HCV genotype-1 subjects; Fig. 1) and when indicated, subgroups analysis was performed using the Mann-Whitney test. To determine whether HCV RNA ($\log_{10}$) levels differ between SVR vs. non-SVR subjects in each time point, we used the two-way analysis of variance (ANOVA).

To determine the discriminatory ability of log10 HCV RNA decline from baseline to identify likely SVR cases, we computed the area under the receiver operator characteristic curve (AUROC) at selected time points during therapy. The area under the receiver operator characteristic curve is a measure of the probability that in a randomly selected pair of SVR and non SVR patients, the marker (in this case, log10 HCV RNA decline from baseline) permits correct identification. We also report the positive and negative predictive values, which quantify the clinical value of a marker. The level of statistical significance was set at ($p \leq 0.05$). All tests were performed by SPSS v.17 Chicago, IL.

Results

Baseline characteristics and viral response

The baseline characteristics of the 26 subjects who were included in the study are presented in Table 1. Five patients discontinued therapy by week 12 (one was incarcerated, one died due to a complication not related to liver disease, two asked to stop treatment, and one was lost to follow-up). At the end of therapy, i.e., week 48, 18 (out of 21) achieved an end-of-treatment response (HCV RNA <50 IU/ml), while only seven patients had an SVR (Tables 2 and 3). Considering baseline characteristics (Table 1), HCV genotype was the only parameter associated with SVR based on intention to treat (ITT) p=0.09 and per protocol (PP) p=0.05 analysis.

Viral kinetic profiles and response

Viral response by genotype is presented in detail at 0-28 days and 0-84 days of therapy for the 21 patients with complete follow-up (Fig. 1). Patients were stratified into three groups based on their viral response (i.e., NR – nonresponders [i.e., detectable HCV RNA at the end of therapy (week 48); REL – relapsers [i.e., negative HCV RNA at week 48 but positive after follow up], SVR [i.e., negative HCV RNA at follow up] (Fig. 1). It is clear that regardless of the genotype, the viral load decay pattern at early on treatment time points distinguished among the SVR, REL and NR groups. There were distinct differences in the

response pattern between genotype 1 (Figures 1A & 1B) and genotype 3 (Figures 1C & 1D). Patients infected with HCV genotype 3, including those in the REL group, showed a more rapid and intense initial reduction in viral load than that seen in patients infected with HCV genotype 1. Genotype 1 subjects who achieved an SVR had a fast and marked viral decline, which distinguished them from REL or NR. In genotype 1 patients, a 1.5 log drop at day 15 differentiated SVR from REL (p=0.012) and 1.9 log drop at day 15 distinguished SVR from NR (p=0.008). For genotype 3, a 1.5 log drop by week 4 distinguished between SVR and REL (p=0.014) even though all genotype 3 patients reached cEVR.

Viral kinetic parameters during the first 29 days of therapy in all 26 patients are presented in Table 2. Following the first dose of PEG-IFN, viral load dropped to a nadir, V_{min}, of 1.3 ± 0.3 log10 from baseline within 1.6 ± 0.3 days (Table 2). Thereafter, a 0.3-to **12**.9-fold viral rebound was observed before the second dose of PEG-IFN was given at day 7. Following the second dose of PEG-IFN, a slower phase of viral decline was observed (Fig. 1). While baseline viral load, day of V_{min}, and viral rebound parameters were similar among the SVR, REL and NR groups, the first phase of viral decline from baseline and the viral slope decline (i.e., following the second dose of PEG-IFN) were significantly ($p<0.02$) higher in SVR compared to REL and NR (Table 2).

Viral kinetic profiles, HCV genotype, race and response

We further analyzed viral response in conjunction with genotype as shown in Table 3. First-phase viral decline was significantly higher in genotype 3 compared to genotype 1 patients (median 0.92 vs 1.65 $\log_{10}$, respectively, p=0.009). In addition, the slower-phase viral decline slope measured from day 7 until day 15 (median 1.0 vs 0.35 log/wk, respectively, p=0.031) or from day 7 until day 29 (0.72 vs 0.30 log/wk, respectively, p=0.008), were significantly higher in genotype 3 compared to genotype 1. All rapid viral responder (RVR) subjects were genotype 3 (p=0.007). At week 12, all genotype 3 subjects had a cEVR, while only 20% of genotype 1 ($p<0.001$) subjects achieved a cEVR. End-of-therapy response and relapse rate were similar by genotype (p=0.3 and p=0.1, respectively), but SVR rate was significantly (p=0.05) greater in genotype 3 patients. Interestingly, viral kinetic parameters and treatment response did not vary by race/ethnicity (White or Black) (not shown).

Finally, the relationship between $\log_{10}$ viral decline at days 2 and 15 per genotype and outcome of therapy is shown in Fig. 2. Patients who achieved an SVR had a profound viral decline (see left lower quadrant of Fig. 2). In contrast, relapsers (REL) and nonresponders (NR), scattered on the two upper quadrants, which corresponds to a slower pattern of viral decline slope (see also Table 2).

Very early predictors of successful treatment response

Change in HCV RNA level at very early on treatment time points was a strong predictor of SVR. In genotype 1 patients, an HCV RNA decline of 0.75 $\log_{10}$ from baseline at day 1, had good discriminatory ability (AUROC 0.95), a positive predictive value (PPV) of 67% and a negative predictive value (NPV) of 100% for SVR (Table 4). In the genotype 3 group, a day 2 HCV RNA decline cutoff value of 0.97 $\log_{10}$, had a good discriminatory ability (AUROC 0.82), with a PPV of 83% and NPV of 100% for the development of SVR (Table 4). In both groups, viral decline at day 2 had similar discriminatory ability with the same PPV and NPV to identify likely SVRs as RVR at week 4 (Table 4). According to these criteria, 2 out of 3 (67%) genotype-3 subjects and 10 out of 11 (91%) genotype-1 subjects, could have stopped (or extended) therapy based on day 2 HCV RNA decline.

Coinfected patients with a slow second phase viral decline slope less than 0.3 log/wk (measured here from day 2 to day 29 using linear regression; Table 2) did not achieve SVR

(NPV=100%), in agreement with publications in both HCV genotype 1-monoinfection and HIV/HCV coinfection patients [21,22,28,29]. However, the positive predictive value for the second phase slope was low in both genotypes (PPV=67% in genotype 1 and PPV=71% in genotype 3), consistent with a recent study in coinfected patients [22]. According to these criteria, 1 out of 3 (33%) genotype-3 subjects and 10 out of 11 (91%) genotype-1 subjects, could have stopped (or extended) therapy at day 2.

Discussion

In this detailed viral kinetic study, we found that HIV/HCV coinfected patients who were treated with PEG-IFN-α-2a and ribavirin had nadir HCV RNA, V_{min}, 1.6 ± 0.3 days which was followed by 0.3- to 12.9-fold viral rebound (until the administration of the second dose of PEG-IFN at day 7) regardless of genotype or outcome of therapy. This viral rebound is likely related to the PEG-IFN pharmacokinetic and pharmacodynamic features as recently shown using mathematical modeling [23,24,27]. These viral kinetic features were not associated with SVR and HCV genotype and may suggest that first phase viral decline (i.e., viral nadir) under PEG-IFN-α-2a can be estimated in future studies between 1 to 2 days post initiation of therapy.

Current therapeutic guidelines suggest the discontinuation of therapy based on failure to achieve a pEVR at week 12 [30]. Recently, the RVR at week 4 was found to be highly associated with SVR in coinfected patients [17-19]. Early prediction of nonresponse to pegylated-interferon/RBV is particularly important in HIV/HCV coinfected patients to permit early treatment discontinuation in those who are unlikely to respond. Here we found that the first phase viral decline from baseline and a slower phase decline slope (between day 7 and day 29) were associated ($p<0.05$) with SVR and were significantly ($p<0.01$) higher in genotype 3 than in genotype 1 subjects (Tables 2 and 3), in agreement with previous viral kinetic studies in patients mono-infected with HCV genotype 1 or genotype 3 [21,31-34]. In addition, a *second phase* viral decline slope (i.e., measured from day 2 till day 29) less than 0.3 log/wk has a NPV of 100% for SVR. Perhaps even more importantly, day 2 viral response had similar predictive values of nonresponse as week 4 (Table 4). These results suggest that HCV RNA at day 2 of therapy could potentially identify patients who likely will not achieve SVR. Our results are in line with a recent publication [35] in which a similar very early predictor of noresponse at day 2 was identified in HCV monoinfected patients.

We did not find viral kinetic parameters or viral response patterns that differed by race/ethnicity in our analysis of patients in Brazil. Interestingly, HIV/HCV-coinfected African American patients exhibit significantly smaller declines in HCV RNA than non-Hispainc Whites [23,24]. The same pattern was also found in African American vs. non-Hispanic Whites who were mono-infected with HCV [36,37]. Recently, a genetic polymorphism near the *IL28B* gene, was associated with an approximately twofold change in response to treatment, with substantially greater frequency in European than African populations [38]. Very recently, Howell et al. [39] showed that compared to Caucasians, African Americans had a less vigorous decline of serum HCV RNA from day 0-2 (phase 1) and day 7-28 (phase 2) of early HCV kinetics ($p < 0.01$). Since in the current study there was no significant ($p=0.5$) difference in IL28B genotype frequencies between Black and white race/ethneicty (manuscript in preparation), it may partly explain the lack of association between race/ethnicity and viral kinetic parameters or viral response patterns. Larger studies are needed to provide a comprehensive viral kinetic comparison by race/ethnicity in South America, where patient ancestry may differ from that in the United States.

In a recent publication, we identified several PEG-IFN pharmacodynamic parameters that might identify likely SVR patients early in treatment via mathematical modeling [27]. Here, in order to identify other promising early predictors of successful treatment outcome, that can be easily addressed in future clinical settings, we evaluated the predictive value of early changes in serum HCV RNA levels relative to baseline, for its potential to identify likely nonresponders. As previously suggested in HCV monoinfection [34,40], we found that a viral decline <1.19 log for genotype 1 and <0.97 log for genotype 3, respectively, had NPV of 100% for SVR as early as day 2 post initiation of therapy. The high negative predictive value at day 2 minimizes the likelihood of premature treatment discontinuation in patients who might achieve a successful therapeutic outcome. Notably, as we are approaching a new era of therapy with direct antiviral agents, an early prediction of nonresponse to PEG-IFN based therapy may help in designing more effective therapeutic strategies such as the inclusion of direct antiviral agents against HCV [41,42]. Larger studies are needed to verify that these parameters can consistently identify nonresponders at very early time points.

Acknowledgments

The authors thank Fernando F.Tatsch and Lori Brisbin from Roche by the support on drug and tests supplies; Steve Young from Tricore Reference Laboratories for performing HIV and HCV load tests; Claudia Courtouke for helping with the original clinical data;Dr.José Luiz Boechat Paione and Hospital Ana Costa to allow patients hospitalization and blood drew along the clinical phase; LIM-47 team for excellent technical assistance, and the patients and their family members for the trust and participation.

Grant support: Study carried out with the assistance of Roche Laboratories of Brazil, which provided financial support in the form of the pegylated interferon α-2a, kits for molecular assays and the shipping of samples. H.D is supported by the University of Illinois Walter Payton Liver Center GUILD and by NIH grant P20-RR018754.

List of Abbreviations

NPV	negative predictive value
PPV	positive predictive value
ANOVA	analysis of variance
HAART	highly active antiretroviral therapy
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ROC	receiver operating characteristic
SVR	sustained virological response
RVR	Rapid Virologic Response
EVR	Early Virologic Response
NR	Non Responders
EOT	End of Therapy Response
REL	Relapser
ITT	intention to treat
PP	per protocol
Gen	Genotype
NS	not significant
IFN	interferon

STAT-C specifically target HCV therapy

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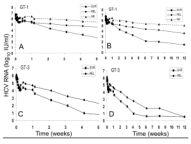

Figure 1.

HCV RNA kinetics per viral response group per genotype. (A) and (C) early viral kinetics from initiation of therapy until day 15, in patients infected with HCV genotype-1 (GT-1) or genotype-3 (GT-3), respectively. (B) and (D) viral kinetics from initiation of therapy until week 12, in patients infected with HCV genotype-1 (GT-1) or genotype-3 (GT-3), respectively. * For difference between XXX and XXX (p<xxx). ** For difference between XXX and XXX (p<xxx). Vertical lines represent standard error of the mean. Already at day 15, patients who achieved SVR and were infected with HCV genotype 1 had significantly lower viral load than patients who were relapsers (REL) or nonresponders (NR) (p=0.012 and p=0.008, respectively). Among Gen 3 patients, viral load in SVR patients was significantly (p=0.014) lower than REL patients at day 29.

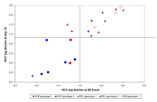

Figure 2.
A relationship between viral decline at days 2 and 15 of therapy per genotype and outcome (see also Table 2).

Table 1

Demographic and basal data.

Gender, n (%) Male / Female	23 (88%) / 3 (12%)
Mean age [yr]	41 (range, 32–56)
Race, n (%) White / Black or mixed	14 (54%) / 12 (46%)
Mean weight [kg]	69 (range, 52 – 92)
Mean CD4 [cells/mm^3]	570 (range, 327–956)
HAART[@] n (%) on / off	18 (69%) / 8 (31%)
Mean HIV viral load [copies/mL]	2215 (range, 170–9930)
Mean HCV viral load [IU/mL]	2,039,492 (range, 1380–10,500,000)
HCV genotype n (%) 1 / 3	15 (58%) / 11 (42%)
Cirrhosis (metavir F4)	4 (15%)

[*] Values per patient are shown in Table 1 of [27];

[@] Only patients with low CD4 (<XXX cells/mm^3) and/or high HIV RNA (>xxx cp/ml) were on HAART.

Table 2

Early Viral Kinetic parameters results

GROUP	Patient No.	Genotype	Baseline HCV RNA (V_0) log(IU/ml)	First-phase viral decline $Log_{10}(V_0/Vmin)$	Vmin (day)	Viral rebound (V_7 / V_{min}) [min - max]	Viral slope decline from day 2 to day 29 [log /wk]	Viral slope decline from day 7 to day 15 [log /wk]	Viral slope decline from day 7 to day 29 [log /wk]
1	1	3	6.2	1.88	2	0.3	1.12	0.82	1.11
1	2	3	5.8	1.57	1.5	1.7	0.98	1.18	1.01
1	3	3	5.2	1.67	1.5	2.2	0.48	0.41	0.62
1	6	3	5.0	1.47	1.75	7.3	0.72	1.77	0.73
1	7	3	6.0	1.49	1	1.0	1.25	1.21	1.40
1	4	1	7.0	2.26	1.75	2.3	0.36	0.65	0.38
1	5	1	6.3	1.35	1.5	0.9	0.98	1.28	1.00
1:	**Mean**±SD		**5.9±0.7**	**1.67±0.31** *a*	**1.6±0.3**	**0.3 - 7.3**	**0.84±0.33** *g*	**1.05±0.45** *c*	**0.89±0.34** *e*
2	8	3	5.6	1.36	1.25	2.9	0.52	0.40	0.58
2	9	3	6.1	2.09	2	2.0	1.38	1.53	1.54
2	13	3	6.1	0.54	1.75	7.8	0.08	(0.28)	(0.02)
2	10	1	5.3	1.03	1	1.2	0.29	0.35	0.30
2	11	1	5.7	0.64	1.75	1.6	0.54	0.26	0.40
2	12	1	5.3	2.04	1.75	1.8	0.28	(0.03)	0.34
2	14	1	6.5	0.43	1.75	1.4	0.08	(0.06)	0.12
2	15	1	5.7	0.76	1.5	1.3	0.24	0.57	0.13
2	16	1	6.4	1.36	1.75	1.5	0.11	0.20	0.18
2	17	1	6.7	1.35	1.5	9.5	0.12	0.42	0.30
2	18	1	6.6	0.00	2	1.0	0.06	0.29	0.07
2:	**Mean**±SD		**6.0±0.5**	**1.05±0.66** *b*	**1.6±0.3**	**1.0 - 9.5**	**0.34±0.39** *h*	**0.33±0.47** *d*	**0.36±0.43** *f*
3	19	1	6.5	0.17	2	1.3	0.26	0.16	0.35
3	20	1	6.8	0.92	1.5	6.2	0.20	0.67	0.24
3	21	1	6.1	0.59	1.25	4.0	0.04	(0.02)	0.03
3:	**Mean**±SD		**6.5±0.3**	**0.56±0.37** *b*	**1.6±0.4**	**1.3 - 6.2**	**0.17±0.11** *h*	**0.27±0.36**[d*]	**0.21±0.16** *f*
4	24	3	3.1	1.67	1.25	0.5	1.68	2.31	2.31[$]

GROUP	Patient No.	Genotype	Baseline HCV RNA (V_0) log(IU/ml)	First-phase viral decline $Log_{10}(V_0/Vmin)$	Vmin (day)	Viral rebound (V_7 / V_{min}) [min - max]	Viral slope decline from day 2 to day 29 [log /wk]	Viral slope decline from day 7 to day 15 [log /wk]	Viral slope decline from day 7 to day 29 [log /wk]
4	25	3	6.0	2.26	1.5	0.7	0.41	0.47	0.30
4	26	3	6.1	0.63	1.25	2.9	0.67	1.19	0.70
4	22	1	6.4	1.65	1.5	1.1	0.54	1.13	0.39
4	23	1	6.5	1.46	1.5	12.9	0.58	0.90	0.58
4:	**Mean**±SD		**5.6±1.4**	**1.53±0.59**	**1.4±0.1**	**0.5 - 12.9**	**0.56±0.03**	**1.01±0.16**	**0.49±0.14**
All	**Mean**±SD	**All**	**6.0±0.8**	**1.26±0.64**	**1.6±0.3**	**0.3 – 12.9**	**0.54±0.45**	**0.68±0.62**	**0.51±0.42**

Groups' definition: 1) SVR, 2) REL, 3) NR as defined in Results and 4) discontinued therapy group; SD, one standard deviation; V_{min}, viral nadir during the first week of treatment; V_7, viral load at day 7;

$ calculated till day 15 due to negative HCV RNA from day 15 onwards;

() represent viral increase;

a, groups marked with the same superscript letter were not significantly different from each other (P>0.05), but they were significantly different (P< 0.02; Kruskal Wallis and Mann-Whitney Tests) from all the other groups in the same column.

b, groups marked with the same superscript letter were not significantly different from each other (P>0.05), but they were significantly different (P< 0.02; Kruskal Wallis and Mann-Whitney Tests) from all the other groups in the same column.

c, groups marked with the same superscript letter were not significantly different from each other (P>0.05), but they were significantly different (P< 0.02; Kruskal Wallis and Mann-Whitney Tests) from all the other groups in the same column.

d, groups marked with the same superscript letter were not significantly different from each other (P>0.05), but they were significantly different (P< 0.02; Kruskal Wallis and Mann-Whitney Tests) from all the other groups in the same column.

e, groups marked with the same superscript letter were not significantly different from each other (P>0.05), but they were significantly different (P< 0.02; Kruskal Wallis and Mann-Whitney Tests) from all the other groups in the same column.

f, groups marked with the same superscript letter were not significantly different from each other (P>0.05), but they were significantly different (P< 0.02; Kruskal Wallis and Mann-Whitney Tests) from all the other groups in the same column.

g, groups marked with the same superscript letter were not significantly different from each other (P>0.05), but they were significantly different (P< 0.02; Kruskal Wallis and Mann-Whitney Tests) from all the other groups in the same column.

h, groups marked with the same superscript letter were not significantly different from each other (P>0.05), but they were significantly different (P< 0.02; Kruskal Wallis and Mann-Whitney Tests) from all the other groups in the same column.

d*, stands for a trend (p=0.065) with SVR group.

Table 3

Virological response and HCV genotype

Viral response parameter	All (n = 26)	Genotype-1 (n=15)	Genotype-3 (n=11)	P value*
1st phase viral decline, median [$Log_{10}(V_0/V_{min})$] and (IQR)		0.92 (0.93)	1.65 (0.68)	0.009
slower phase slope decline (d7-d15), median [log/wk] and (IQR)		0.35 (0.51)	1.0 (0.88)	0.031
slower phase slope decline (d7-d29), median [log/wk] and (IQR)		0.30 (0.26)	0.72 (0.67)	0.008
RVR, <10 IU/ml at W4, n (%)				
Yes	5 (19)	0 (0)	5 (45)	
No	21 (81)	15 (100)	6 (55)	0.007
cEVR@, <10 IU/ml at W12, n(%)				
Yes	13 (52)	3 (20)	10 (100)	
No	12 (48)	12 (80)	0 (0)	<0.001
pEVR@, ≥2log decline at W12, n (%)				
Yes	20 (80)	10 (67)	10 (100)	
No	5 (20)	5 (33)	0 (0)	0.06
EOT @, <100 IU/ml at W48, n (%)				
Yes	18 (85)	10 (77)	8 (100)	0.3
No	3 (15)	3 (23)	0 (0)	
REL@, >50 IU/ml at W24 follow up , n (%)				
Yes	11 (61)	8 (80)	3 (37)	0.1
No	7 (39)	2 (20)	5 (63)	
SVR @, <50 IU/ml at W24 follow up, n (%)				
Yes	7 (33)	2 (15)	5 (62)	0.05
No	14 (67)	11 (85)	3 (38)	

RVR, rapid viral response ; cEVR, complete early viral response; EOT, end of treatment response; REL, relapse during follow up; SVR, sustained viral response; V_{min}, viral nadir during the first week of treatment (see Table 2); V_0, viral load at baseline;

@One patient discontinued treatment from week 11 and four patients after week 12.

*p≤0.05 for a difference between Gen 1 and Gen 3. IQR, Interquartile range

Table 4

Summary of ROC curve cut-off for selected early points and prediction of therapy outcome by HCV genotype.

Genotype	Day/Week	Viral decline cut-off (log_{10} decay)	Area Under the Curve	Sensitivity	Specificity	PPV	NPV
1	d1	0.75	0.95	100%	91%	67%	100%
	d2	1.19	0.95	100%	91%	67%	100%
	w4	1.90	0,95	100%	91%	67%	100%
3	d1	1.30	0.80	60%	91%	100%	60%
	d2	0.97	0.83	100%	67%	83%	100%
	w4	2.00	0.750	100%	50%	83%	100%

PPV, positive predictive value; NPV, negative predictive value.