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**This is the author's manuscript**

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/1633459> since 2021-05-15T07:07:38Z

*Published version:*

DOI:10.1016/j.meegid.2017.03.014

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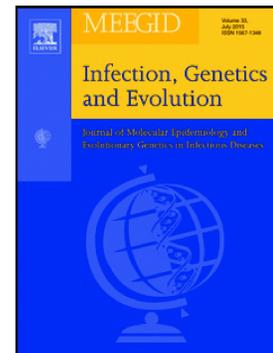
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## Accepted Manuscript

Treatment with PEG-IFN and ribavirin in patients with chronic hepatitis C, low grade of hepatic fibrosis, genotype 1 and 4 and favorable IFNL3 genotype: A pharmacogenetic prospective study

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PII: S1567-1348(17)30085-0  
DOI: doi: [10.1016/j.meegid.2017.03.014](https://doi.org/10.1016/j.meegid.2017.03.014)  
Reference: MEEGID 3094

To appear in: *Infection, Genetics and Evolution*

Received date: 5 December 2016  
Revised date: 8 March 2017  
Accepted date: 14 March 2017

Please cite this article as: Lucio Boglione, Chiara Simona Cardellino, Jessica Cusato, Amedeo De Nicolò, Giuseppe Cariti, Giovanni Di Perri, Antonio D'Avolio, Treatment with PEG-IFN and ribavirin in patients with chronic hepatitis C, low grade of hepatic fibrosis, genotype 1 and 4 and favorable IFNL3 genotype: A pharmacogenetic prospective study. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Meegid(2017), doi: [10.1016/j.meegid.2017.03.014](https://doi.org/10.1016/j.meegid.2017.03.014)

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**TITLE:** Treatment with PEG-IFN and ribavirin in patients with chronic hepatitis C, low grade of hepatic fibrosis, genotype 1 and 4 and favorable *IFNL3* genotype: a pharmacogenetic prospective study.

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**Words (abstract):** 219

**Words:** (excluding references, tables, and figure legends): 2550

**Number of Figures and Tables:** 5 figures and 3 tables

**Running title:** PEG-IFN and RBV in genotype 1 and 4

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**List of Abbreviations:** chronic hepatitis C (CHC); Hepatitis C virus (HCV); pegylated interferon alpha (PEG-IFN- $\alpha$ ); interferon lambda 3 (*IFNL3*), interleukin (*IL*); direct-acting antiviral agents (DAAs); ribavirin (RBV); genotype 1 (GT1); genotype 4 (GT4); sustained virological response (SVR); null responder (NR); partial responder (PR) relapser (REL); inter-quartile range (IQR); Odds Ratio [OR].

**Conflicts of interest:** The authors disclose no conflicts.

**Ethical Approval:** "Ribaveritas" approved by Ethical Committee "A.O.U. S. Luigi Gonzaga, Orbassano, Turin", n°. 45/2014

**Funding:** this study was not supported.

**ABSTRACT**

The new direct-acting antiviral agents (DAAs) rapidly changed the treatment approach in chronic hepatitis C (CHC); however, the interferon (IFN)-free therapies availability is currently different in some countries, due to higher costs of these drugs. Naïve treated patients, who are not eligible for IFN-free therapies, could be selected for standard dual treatment with pegylated (PEG)-IFN and ribavirin (RBV), through *IFN lambda 3* gene polymorphisms and fibrosis stage evaluation.

Inclusion criteria were: naïve treated CHC patients with GT1 or GT4, without major contraindication to PEG-IFN or RBV, with fibrosis stage F0-F2 and *IFNL3* rs8099917/rs12979860 TT/CC genotypes.

65 patients were included in the study. Overall SVR was observed in 50 patients (76.9%); SVR rates among different genotypes were as follows: 15 with GT1a (71.4%), 27 with GT1b (79.4%) and 8 for GT4 (80%). The RBV cutoff at 2 weeks of 1800 ng/mL, predictor of RVR, was determined ( $p=0.003$ ; sensibility=60.4%, specificity=88.2%, positive predictive value=88.9%, negative predictive value=100%). In multivariate analysis, factors significantly associated with treatment failure were living alone condition (OR=4.302; 95%IC=1.254-16.257;  $p=0.034$ ) and RBV plasma level < 1800 ng/mL at 2 weeks (OR=4.970; 95%IC=1.405-17.565;  $p=0.009$ ).

Considering a pharmacogenetic-guided approach, dual therapy with PEG-IFN and RBV can be considered a reliable option for patients ineligible for IFN-free treatments, who are motivated and well informed about all the aspects related to PEG-IFN administration.

**Keywords:** HCV; genotype 1; genotype 4; PEG-IFN; fibrosis; *IL28B*

## 1. INTRODUCTION

In the past two decades, the optimal treatment for chronic hepatitis C infection (CHC) was the combination of pegylated-interferon-alpha (PEG-IFN- $\alpha$ ) and ribavirin (RBV) (McHutchison et al., 1998), though this therapy was less effective in genotype 1 (GT1) and affected by several side-effects (subcutaneous administration and the long term of completion of 24 or 48 weeks) (Antonini et al., 2008; W, 2002). The recent introduction of well-tolerated oral agents (the direct-acting antivirals, DAAs), with a direct suppression of the HCV replication, has completely changed the current approach to CHC treatment. In fact, they can consist in IFN-free regimens, without significant adverse events (AEs), a low pill burden and shorter therapy duration (Carrion et al., 2014). Therefore, to date, PEG-IFN is falling out of use and not indicated as the first-line treatment in the clinical practice guidelines (EASL, 2015). The main limitation of the IFN-free regimens is the high cost, which limits the availability especially in developing countries (Rein et al., 2015); anyway, the restriction policies have also been established in several European states (van de Vooren et al., 2014; Zoulim et al., 2015). In Italy, the Italian Drug Agency (AIFA) approved IFN-free therapies only for patients showing advanced liver fibrosis or cirrhosis, whereas patients showing mild fibrosis stage could be treated only with PEG-IFN and RBV regimens ((AIFA)). Consequently, patients who are not eligible for DAAs may have two options: the first one is to wait a future conceivable extension of inclusion criteria for lower costs of drugs treatment; the second one is to accept the standard treatment. In the latter case, however, the IFN-based treatment should be optimized using an appropriate selection of patients: who may achieve the sustained virological response (SVR), avoiding the IFN administration in presence of poor chances of response, risk of severe side-effects/contraindication or limited compliance.

In a retrospective analysis, we selected GT1 and genotype 4 (GT4) patients considering fibrosis stage, *IFN lambda 3* (*IFNL3*, previously known as *IL28B*) gene genotypes and the rapid virological response (RVR) achievement. In GT1 naïve patients treated for 48 weeks with PEG-IFN and RBV, without severe fibrosis or cirrhosis and *IFNL3* rs8099917/rs12979860 TT/CC genotypes, SVR was 98% (Boglione et al., 2015). In GT4 naïve patients with the same baseline characteristics, SVR was 88.8% (Boglione et al., 2014), with a strong association between the *IFNL3* genotype and the HCV-RNA baseline levels (Boglione et al., 2016).

We decided to analyze *IFNL3* rs8099917/rs12979860 TT/CC, because different studies showed that these two polymorphisms (which are in moderate linkage disequilibrium ( $r^2=0.41$ , in our Italian cohort) were associated with a greater likelihood of HCV persistence, particularly in HCV GT1 and GT4 (Aparicio et al., 2010; Bitetto et al., 2011; Boglione et al., 2015; Boglione et al., 2014).

The main aim of this prospective study was the evaluation of effectiveness of standard dual therapy in GT1 and GT4 naïve treated patients (a real-life population), who are currently not eligible for novel IFN-free regimens, according to fibrosis stage and *IFNL3* gene genotypes.

## 2. METHODS

### 2.1 End-points and study design

This was a prospective, pharmacogenetic, pharmacokinetic single-centre study conducted at the Unit of Infectious Disease, “Amedeo di Savoia Hospital” in Turin, Italy. Patients enrollment started in June 2014 and ended in May 2015. The study protocol was approved by our local Ethic Committee in 23/6/2014 as “In Riba Veritas” study and it was conducted in compliance with the Declaration of Helsinki and with the local Review Board regulations.

Inclusion criteria were: naïve CHC patients with GT1 or GT4, HIV uninfected, without major contraindication to PEG-IFN or RBV, with fibrosis stage F0-F2 (Metavir score) and *IFNL3* rs8099917/rs12979860 TT/CC genotypes. All the patients have been informed of the alternative

option of waiting for the novel IFN-free therapies, when available, and they gave an informed consent before the study inclusion.

All the patients screened for this study provided a questionnaire describing the reason for accepting or refusing treatment.

Primary end-point of this study was the SVR evaluation; secondary aims were the side-effects analysis, the treatment interruption due to toxicity, RBV pharmacokinetic (PK) analysis at selected time-points.

All the patients were treated using PEG-IFN- $\alpha$  2a once-weekly through subcutaneous injection at the dose of 180  $\mu$ g (Pegasys<sup>®</sup>, Roche) or PEG-IFN- $\alpha$  2b 1.5  $\mu$ g/kg/week with RBV at 15 mg/kg/day for 48 weeks. All the patients were followed for 6 months after the treatment completion.

SVR was defined as HCV-RNA undetectable 24 weeks after treatment completion; rapid virological response (RVR) was defined as HCV-RNA undetectable after 4 weeks of therapy; early virological response (EVR) as HCV-RNA negative after 12 weeks. Treatment failure was defined by the lack of SVR: null-responders (NR), when the decrease of HCV-RNA after 12 weeks of therapy was less than 2 log; partial responders (PR), if HCV-RNA decrease was more than 2 log after 12 weeks, but still detectable at week 24; relapsers (REL), when HCV-RNA was undetectable at treatment completion, but positive in the follow-up without re-infection; treatment was discontinued in NR at week 12 and in PR at week 24.

Safety evaluation was performed according to WHO grading scale (WHO, 2003).

HCV-RNA quantification was performed after 1 and 2 weeks and monthly until the end of therapy.

Fibrosis stage was evaluated as METAVIR Fibrosis Score using transient elastography (Fibroscan<sup>®</sup>, Echosens, Paris, France); according to liver stiffness cut-off values reported in Castéra *et al.*: F0<5.0 kPa; F1: 5.1-7.0 kPa; F2: 7.1-9.4 kPa; F3: 9.5-12.4 kPa; F4>12.5 kPa (Castera *et al.*, 2005).

## 2.2 Pharmacogenetic analysis

*IFNL3* rs8099917 and rs12979860 polymorphisms were determined with Taq Man Drug Metabolism Genotyping Assays (TaqMan MGM probes, FAM and VIC dye-labeled, Applied Biosystems by Life Technologies, Carlsbad, California, US), using a real-time polymerase chain reaction allelic discrimination system (Bio-Rad Real-time thermal cycler CFX96), with a standard procedure (primers, probes and PCR conditions available on request).

## 2.3 Pharmacokinetic analysis

RBV plasma level measurement was performed at the end of dosing interval, before the assumption of the new dose ( $C_{\text{trough}}$ ) at 1 and 2 weeks of treatment and then monthly, until 6 months of therapy. RBV quantification has been performed through a previously published HPLC-UV method (D'Avolio et al., 2006).

## 2.4 Statistical analysis

PK data have been described as median values and interquartile ranges (IQR).

Differences between two groups have been tested through non parametric Mann-Whitney test. Intra-patient differences at different timings have been evaluated through Wilcoxon test for paired samples.

Correlations between continuous variables have been evaluated by bivariate Pearson correlation test, whereas Spearman one was considered for correlations between ordinal categorical and continuous variables. Univariate logistic regression has been performed in order to test the role of single variables for treatment failure: only variables with a P value lower than 0.2 have been tested in the multivariate analysis. P values lower than 0.05 have been considered statistically significant. Finally, receiver operating characteristic (ROC) curve has been used in order to

determine RBV cutoff values for RVR. All the statistical tests have been performed through SPSS version 22.0.

### 3. RESULTS

#### 3.1 Patients selection and baseline characteristics

A total of 174 CHC GT1 or GT4 patients were screened in the enrollment period; 41 were excluded for a fibrosis stage > F2, 9 experienced, 27 for a different *IFNL3* genotype compared to TT/CC one and 32 refused the treatment option with PEG-IFN and RBV. Thus, 65 patients were finally included in the study (Figure 1).

Baseline characteristics of the study population were reported in Table 1. Male patients were 47 (72.3%), Italians 42 (64.6%); the most frequent risk factor for HCV detection was intravenous drug use (IDU) in 25 patients (38.5%) with 16 patients on treatment with methadone or buprenorphine (24.6%). Among socio-economic factors, we observed that unemployed subjects were 31 (47.7%), 14 live alone (21.5%), 9 had a previous detention (13.8); median time of schooling was 8 years, with an observed low level in 19 (29.2%). Alcohol consumption was reported in 41 (63%) patients.

Reasons of 32 patients who refused treatment were represented in figure 2: many of them (16, 50%) have chosen to wait new therapies, when available.

#### 3.2 Treatment outcomes

Overall SVR was observed in 50 patients (76.9%); SVR rates among different genotypes were as following: 15 with GT1a (71.4%), 27 with GT1b (79.4%) and 8 for GT4 (80%) (Figure 3).

HCV-RNA was undetectable after 2 weeks of therapy in 13 patients (20%) and RVR was achieved in 7 (10.8%) ones; all the RVR patients at 2 weeks and 1 month gained the SVR. Early virological response (EVR) was observed in 40 patients without RVR (61.5) and 27 of them (67.5%) achieved SVR. The 13 patients without EVR were: 2 (3%) NR (treatment

stopped at 12 weeks), 1 (1.5%) PR (treatment stopped at 24 weeks) and 5 (7.7%) with relapse after treatment completion (Table 2). Other 3 patients interrupted treatment before the 12 weeks (drop-out) for side-effects and poor adherence. The other 4 drop-out patients stopped the treatment after 12 weeks: 2 patients for physicians' decision (grade 2 of anemia with severe symptoms) and 2 for own choice, due to difficult life conditions or professional limitations related to PEG-IFN side-effects.

### 3.3 Side-effects and treatment interruption

The observed side-effects during treatment were described in Table 2. Anemia and neutropenia were the most common laboratory detected abnormalities (20 and 13.8%, respectively); 2 patients with grade 2 anemia interrupted treatment after 12 weeks for clinicians' decision, due to severity of the symptoms (fatigue and movement difficulties). The management of 11 patients with grade 1 anemia has been performed with only RBV dose reduction (n=6), epoetin beta administration (n=2) and with both reduction and growth factors (n=3). Neutropenia was prevalent in patients treated with PEG-IFN- $\alpha$  2a (8 vs 1) and it was solved with dose adjustment from 180 $\mu$ g to 135 $\mu$ g. No serious adverse effects were reported. Flu-like syndrome was the most prevalent self-reported trouble in 28 patients (43%) with associated fatigue (50.7%) and weight loss (27.7%).

5 drop-out patients (3 before and 2 after 12 weeks of treatment) were observed, due to PEG-IFN related side-effects affecting life or job conditions.

### 3.4 RBV pharmacokinetic

RBV plasma concentrations at 1 and 2 weeks were significantly related to HCV-RNA undetectability ( $p < 0.001$ ); median RBV values at 2 weeks of treatment were 1438 ng/mL in patients without undetectable HCV-RNA and 2687 ng/mL in negative HCV-RNA ones ( $p < 0.001$ ) (Figure 4).

Median RBV values at 2 weeks and 1 month of treatment resulted significantly higher in patients who gained SVR compared to patients who failed treatment (Figure 5); at 2 weeks RBV values were: 1849 ng/mL in SVR, 809 ng/mL in NR-PR and 1020 ng/mL in REL patients; at 1 month 1979 ng/mL in SVR, 907 in NR-PR, 1070 in REL ( $p < 0.001$  for all groups) ones.

Finally, receiver operating characteristic (ROC) curve has been used in order to determine the RBV cutoff at 2 weeks of 1800 ng/mL, predictor of RVR ( $p = 0.003$ ; sensibility=60.4%, specificity=88.2%, positive predictive value=88.9%, negative predictive value=100%).

### *3.5 Univariate and multivariate analysis for treatment failure*

We have focused the attention on treatment failure (Table 3), since higher rates of SVR were observed in this study. In univariate analysis, following factors were related to treatment failure: GT1a (OR=2.393; 95%IC=0.761-7.524;  $p = 0.135$ ), living alone condition (OR=4.100; 95%IC=1.169-14.384;  $p = 0.028$ ), RBV level below 1800 ng/mL at 2 weeks of therapy (OR=4.800; 95%IC=1.441-15.993;  $p = 0.011$ ). In multivariate analysis, factors significantly associated with treatment failure were living alone condition (OR=4.302; 95%IC=1.254-16.257;  $p = 0.034$ ) and RBV plasma level < 1800 ng/mL at 2 weeks (OR=4.970; 95%IC=1.405-17.565;  $p = 0.009$ ).

## **4. DISCUSSION**

The current use of dual therapy with PEG-IFN and RBV is often limited by the spread of novel DAAs and IFN-free regimens; however, the problem of high costs of these treatments leads to different availability in many areas of the world, especially in developing countries. Moreover, in most cases, the IFN-free regimens were administered only in patients with advanced hepatic fibrosis or cirrhosis (Chhatwal et al., 2015; Messori et al., 2014). Two different options are now available for patients, who were excluded from new treatments: waiting for future therapies or

the administration of standard dual therapy with PEG-IFN and RBV. Some recent studies examined the patients choices about the treatment decision; interestingly, treated naïve patients, with lower fibrosis stage, accepted treatment more than others. The main cause of treatment refusal in experienced or cirrhotic patients was the fear of IFN-related side-effects (Feillant et al., 2015). Other causes of delayed or refused treatment could be the socio-economic conditions, language barriers or schooling level, and especially the employment status (Niederrau et al., 2012). In our analysis of 32 patients, who refused the PEG-IFN treatment option, the most relevant refusal reasons were the waiting for IFN-free regimens (50%) and the fear of PEG-IFN toxicity (31.2%) (Figure 2). However, our selection excluded the experienced patients with severe hepatic fibrosis and, among 97 screened subjects with all the inclusion criteria, 65 accepted to start treatment (67%).

Treatment desire was more often related to young age, social conditions, patient motivation, ability to understand the most common side-effects and pregnancy planning for female patients, as previously observed in several studies (Shiffman and Benhamou, 2013).

Therefore, dual therapy should be optimized in patients with selected characteristics in order to improve the effectiveness and minimize the problems related to PEG-IFN or RBV administration. Based-on previous analyses in GT1/4 dual therapy treated patients , we identified an increased SVR rate in a population showing the following characteristics: naïve treatment, with *IFNL3* TT/CC genotypes, low fibrosis stage and RVR achievement (Boglione et al., 2015; Boglione et al., 2014). Our results confirmed the effectiveness of dual therapy in this selected population; the overall SVR achievement was similar to that reported in retrospective analyses, despite the presence of drop-out patients. This high rate of response and the global low impact of toxicity on treatment interruption (10.8%) showed that PEG-IFN and RBV can still be a valuable therapeutic option in a selected group. However, the management of side-effects represents an important factor for avoiding treatment interruption; all the patients should be well informed about all the aspects related to PEG-IFN and RBV toxicity and their

consequences in everyday life. Therefore, in our study, we analyzed all the possible socio-economic conditions related to treatment interruption (considering the patient choice). Interestingly, the possible barriers as low schooling level, previous imprisonment, active IDU, unemployed status, methadone or buprenorphine assumption were not predictors of treatment failure, whereas patients who live alone evidenced a higher drop-out risk. This novel finding could be related to difficult PEG-IFN management (as well as subcutaneous administration or the drug storage in the refrigerator) in complicated living conditions. For these reasons, patients who live alone may not be the ideal candidates for this therapy and should waiting for the novel IFN-free regimens, when available.

RBV plasma level pharmacokinetic analysis confirmed the important role of this drug concentrations for RVR and SVR prediction (D'Avolio et al., 2012); consequently, we recommended the RBV weight-based dose (15 mg/Kg/day) and, when possible, the plasma measurement at 2 weeks for dose adjustment, considering a level below the optimal cut-off related to treatment response (1800 ng/mL).

The current use of IFN-based therapies is debated (Feld, 2014); IFN-free regimens are really promising and desirable for higher effectiveness and low toxicity, but in many countries, they are currently unavailable. Therefore, in patients with selected genetics, clinical characteristics and with a strong motivation, the dual therapy administration may be the only current available option in resource-limited settings.

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**Figure legends**

**Figure 1.** Flow of enrolled patients in the study

**Figure 2.** Reasons for treatment refusing

**Figure 3.** Outcomes of treatment according to HCV genotypes

**Figure 4.** RBV median plasma concentration (ng/mL) of treatment in patients with and without HCV-RNA undetectable at 2 weeks of treatment.

**Figure 5.** RBV median plasma concentration (ng/mL) among different virological outcomes

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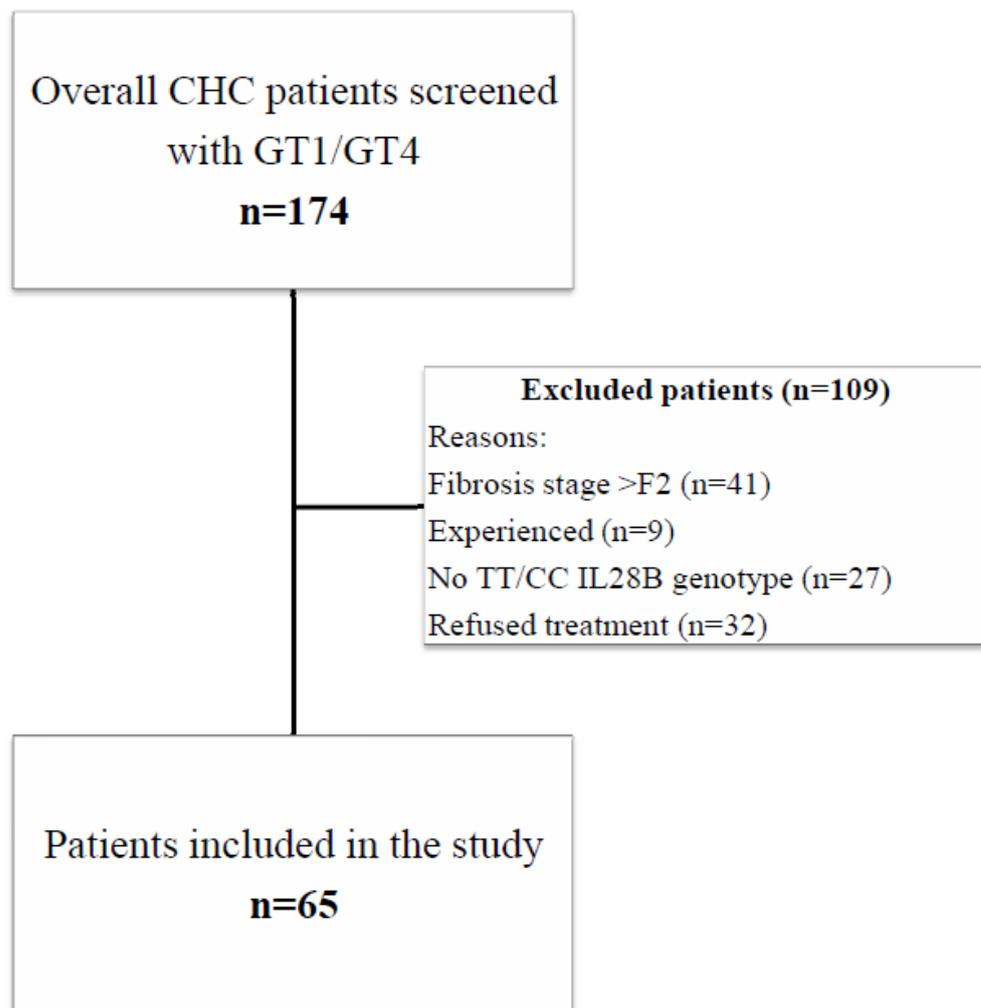


Fig. 1

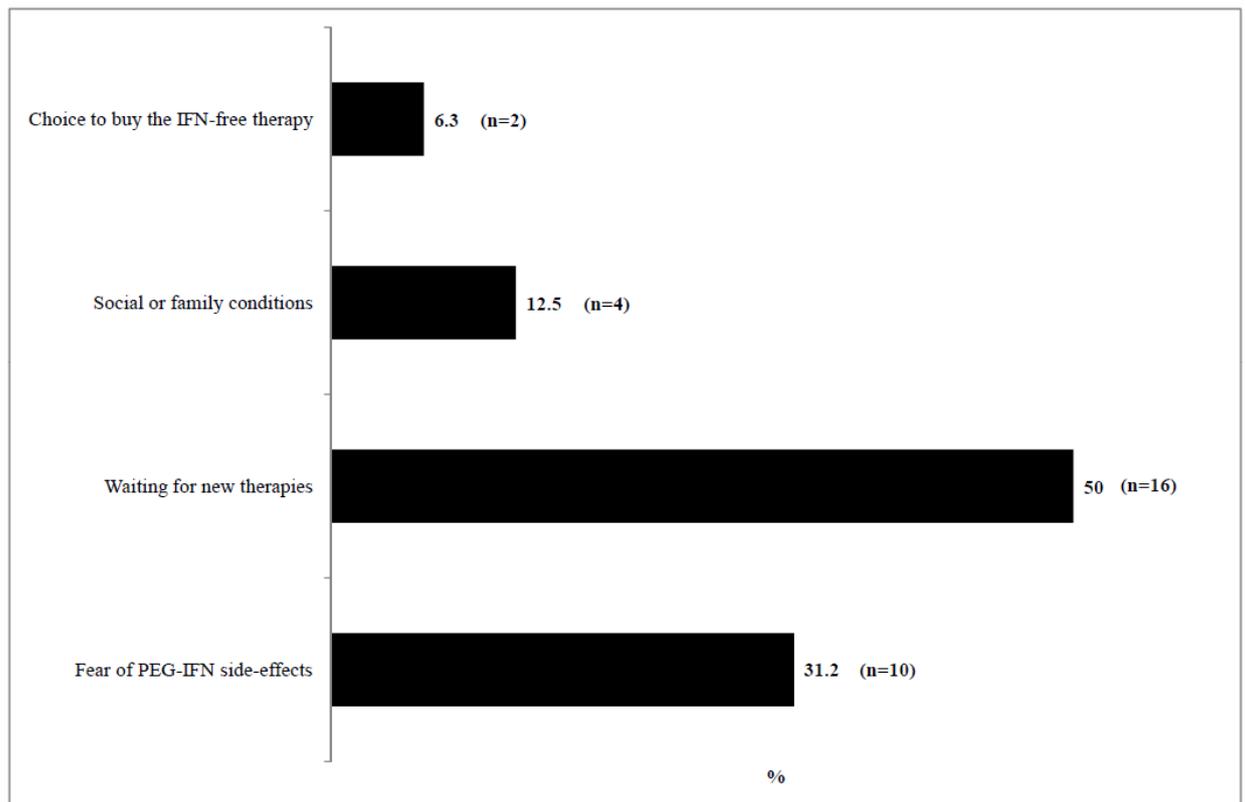


Fig. 2

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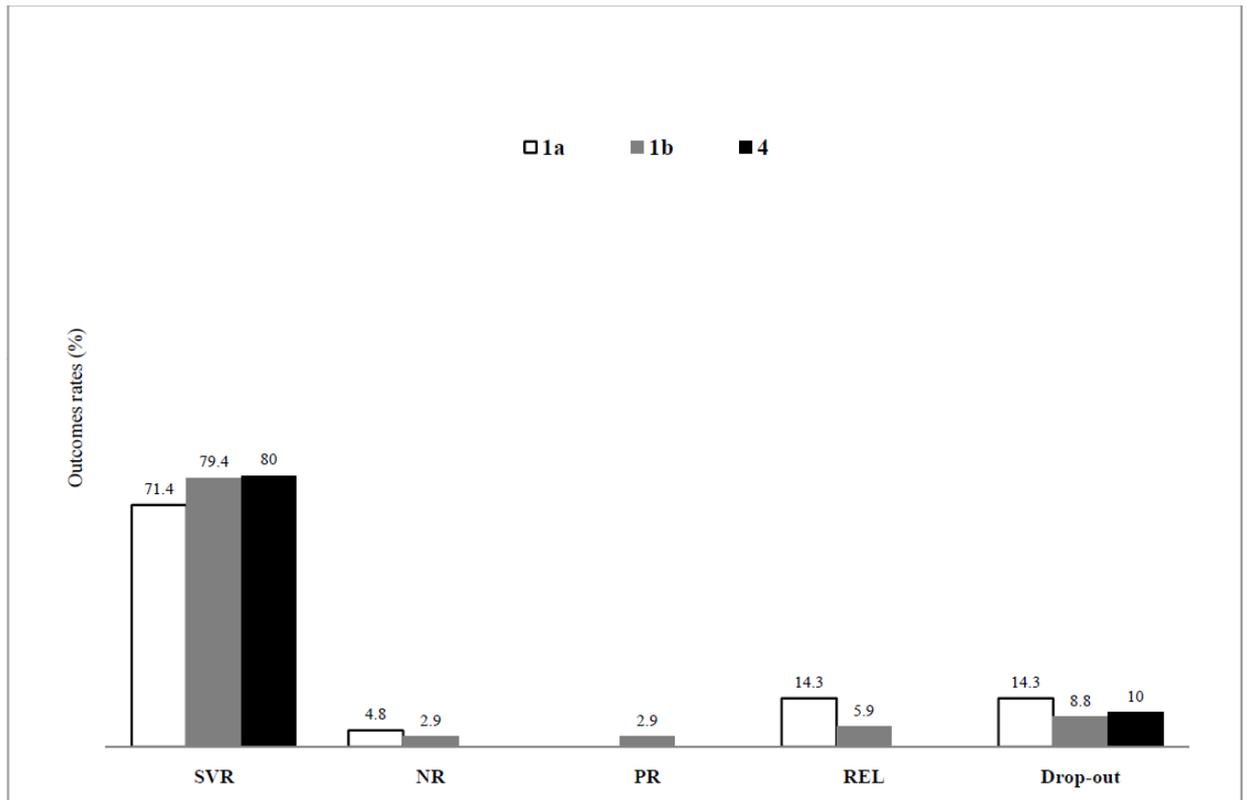


Fig. 3

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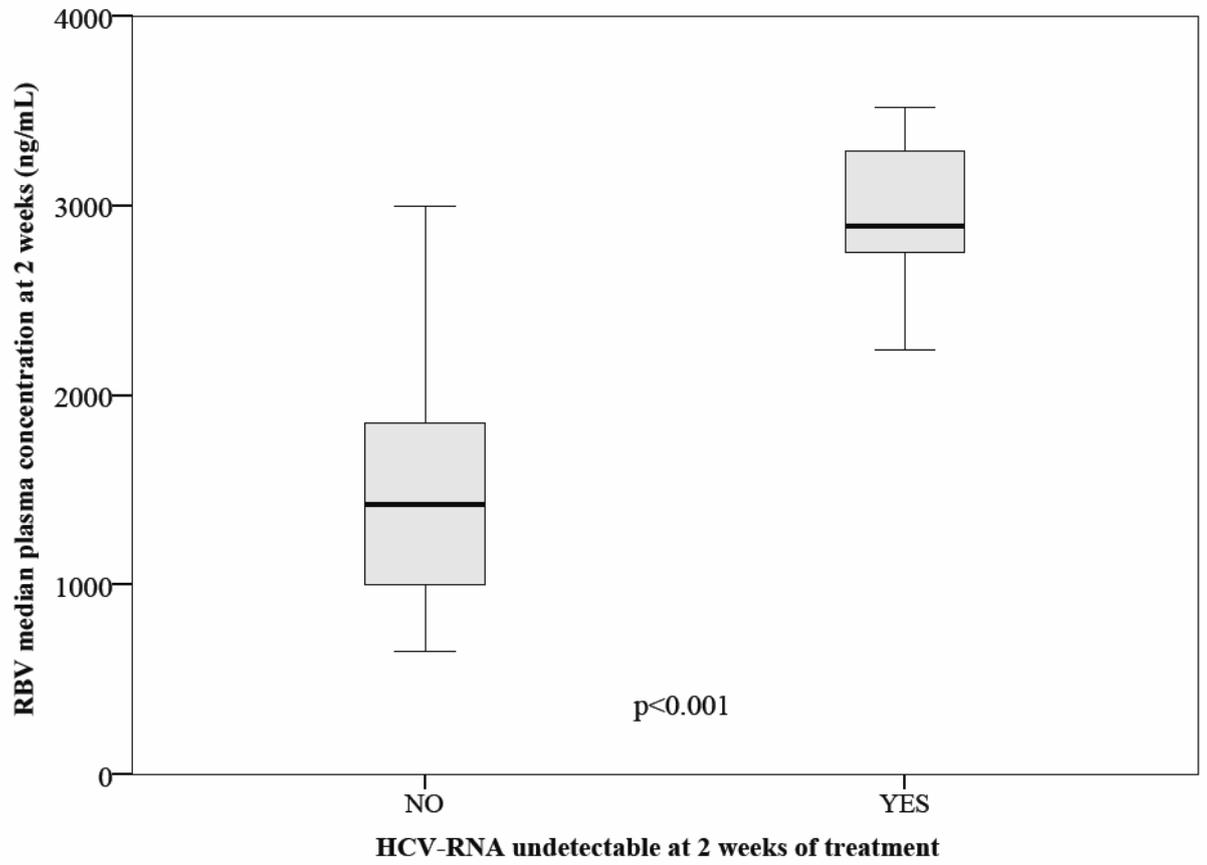


Fig. 4

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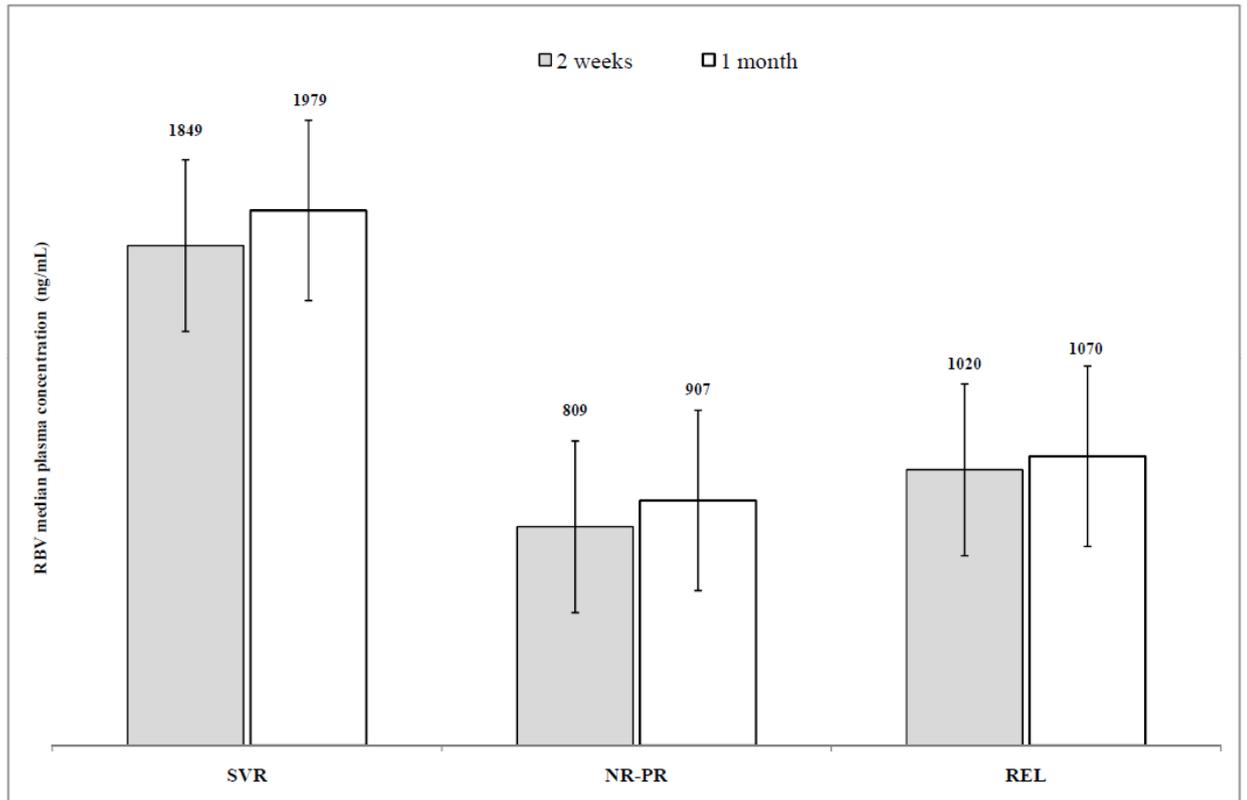


Fig. 5

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**Table 1.** Baseline characteristics of study population

<b>Patients characteristics</b>	<b>N=65</b>
Gender: male, n (%)	47 (72.3)
Age (yr)	43 [35-50.5]
Ethnic group, n (%)	
Italian	42 (64.6)
Egyptian	8 (12.3)
East-Europe	14 (21.5)
Africa	1 (1.5)
Risk factors for HCV n (%)	
Unknown	18 (27.7)
Sexual exposure	8 (12.3)
IDU	25 (38.5)
Blood transfusion	14 (21.5)
Methadone or buprenorphine assumption N (%)	16 (24.6)
Alcohol consumption n (%)	
None	24 (36.9)
< 20 g/day	17 (26.1)
20-50 g/day	16 (24.6)
>50 g/day	8 (12.3)
Years of schooling	8 [5-10.5]
Low schooling level (<5 years)	19 (29.2)
Patients unemployed	31 (47.7)
Patients living alone	14 (21.5)
Patients with previous detention	9 (13.8)
BMI (kg/m <sup>2</sup> )	25 [22.8-27.1]
BMI>25	33 (50.8)
BMI>30	4 (6.2)
Liver stiffness (kPa)	6.7 [5.2-7.8]
Fibrosis stage [Metavir score], n (%)	
0	13 (20)
1	45 (69.2)
2	7 (10.8)
Alanine aminotransferase (ALT) [IU/ml]	75 [43-121]
HCV genotypes n (%)	
1a	21 (32.3)
1b	34 (52.3)
4	10 (15.4)
HCV-RNA [LogIU/ml]	6.1 [5.6-6.4]
HCV-RNA>600.000 IU/mL	43 (66.2)
Cryoglobulinemia n (%)	30 (46.2)
Insuline resistance n (%)	22 (33.8)
Diabetes n (%)	9 (13.8)
PEG-IFN $\alpha$ -2a	41 (63.1)
Dose: 180 $\mu$ g/week	41 (63.1)
PEG-IFN $\alpha$ -2b	24 (36.9)
Dose: 50 $\mu$ g/week	1 (1.5)
80 $\mu$ g/week	8 (12.3)

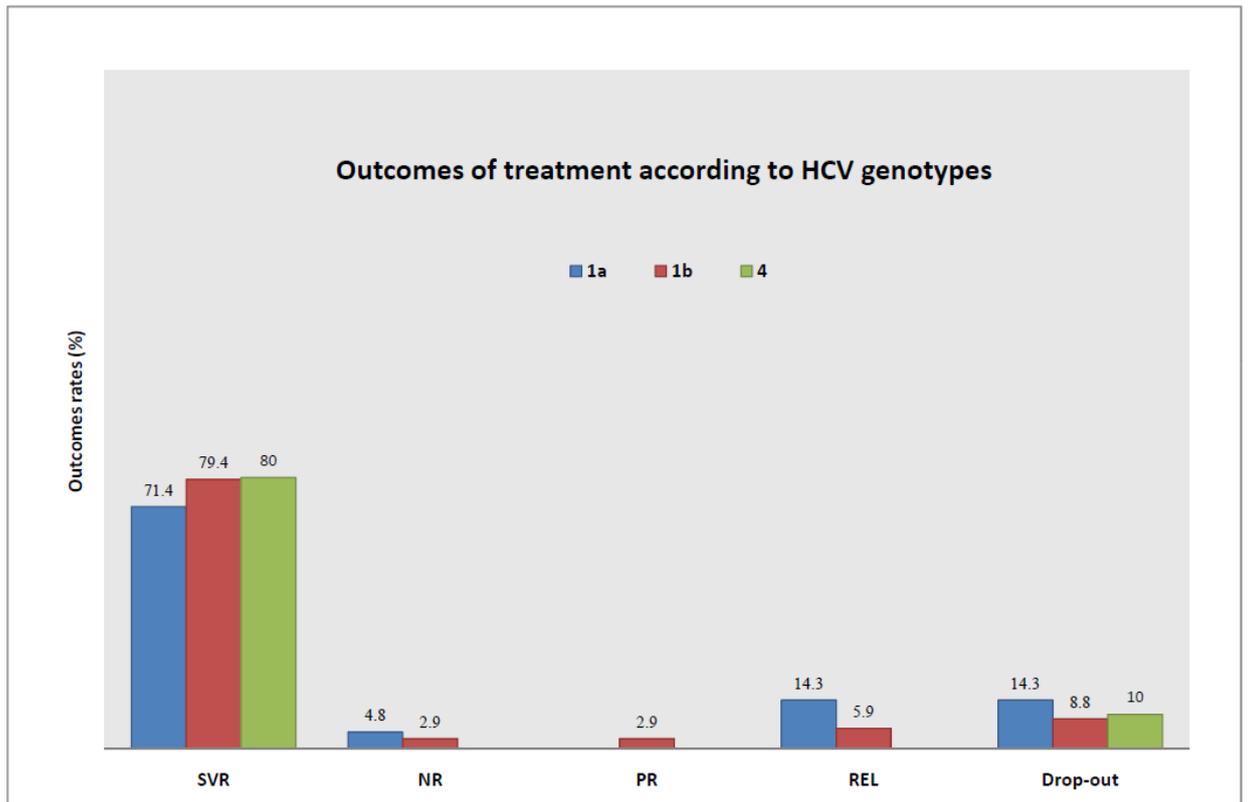
100µg/week	4 (6.2)
120µg/week	7 (10.8)
150µg/week	4 (6.2)
<b>Ribavirin dose (mg/day)</b>	
800 mg	16 (24.6)
1000 mg	34 (52.3)
1200 mg	13 (20)
1400 mg	2 (3.1)

**Table 2.** Treatment outcomes, laboratory abnormalities and side-effects observed in the study population

<b>Outcome</b>	<b>N, %</b>
HCV-RNA undetectable at 2 weeks	13 (20)
RVR	7 (10.8)
EVR	40 (61.5)
SVR	50 (76.9)
Null-responders	2 (3)
Partial-responders	1 (1.5)
Relapser	5 (7.7)
Drop-out	7 (10.8)
<b>Laboratory abnormalities and side-effects</b>	<b>N, %</b>
Anemia, any grade	13 (20)
Grade 1	11 (16.9)
Grade 2	2 (3)
Neutropenia, any grade	9 (13.8)
Grade 1	6 (9.2)
Grade 2	3 (4.6)
Flu-like syndrome	28 (43)
Fatigue	33 (50.7)
Anxiety, depression, insomnia	8 (12.3)
Weight loss	18 (27.7)
Hair loss	8 (12.3)

**Table 3.** Univariate and multivariate analysis for treatment failure

<b>Univariate analysis</b>	
<b>Factors</b>	<b>OR, 95% IC, <i>p</i></b>
Age >50	1.835 (0.522-6.098) <i>p</i> =0.322
Sex M	0.611 (0.186-2.009) <i>p</i> =0.417
<b>Genotype 1a</b>	<b>2.393 (0.761-7.524) <i>p</i>=0.135</b>
High viral load	0.649 (0.207-2.036) <i>p</i> =0.459
PEG-IFN alfa (2a vs 2b)	1.276 (0.411-3.962) <i>p</i> =0.673
Italian origin	1.440 (0.436-4.761) <i>p</i> =0.550
Active IDU	0.833 (0.263-2.631) <i>p</i> =0.755
BMI >25	1.553 (0.507-4.757) <i>p</i> =0.441
Insuline resistance	1.091 (0.341-3.486) <i>p</i> =0.883
Diabetes	1.500 (0.331-6.805) <i>p</i> =0.599
Low schooling level	1.469 (0.451-4.784) <i>p</i> =0.524
Previous imprisonment	1.534 (0.315-5.908) <i>p</i> =0.533
Unemployed	1.035 (0.342-3.134) <i>p</i> =0.951
<b>Living alone</b>	<b>4.100 (1.169- 14.384) <i>p</i>=0.028</b>
Methadone or buprenorphine	1.402 (0.405-4.851) <i>p</i> =0.594
<b>[RBV] at 2 weeks of therapy &lt; 1800 ng/mL</b>	<b>4.800 (1.441-15.993) <i>p</i>=0.011</b>
<b>Multivariate analysis</b>	
<b>Factors</b>	<b>OR, 95% IC, <i>p</i></b>
Genotype 1a	1.953 (0.550-6.942) <i>p</i> =0.301
<b>Living alone</b>	<b>4.302 (1.254-16.257) <i>p</i>=0.034</b>
<b>[RBV] at 2 weeks of therapy &lt; 1800 ng/mL</b>	<b>4.970 (1.406-17.565) <i>p</i>=0.009</b>



Graphical abstract

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## Highlights

- The IFN-free therapies are currently not available for all patients due to higher costs.
- The standard dual therapy with PEG-IFN and RBV could be use in selected patients who are ineligible for IFN-free regimens.
- In naïve patients with genotypes 1a, 1b or 4, F0-F2 and IL28B TT/CC the higher chance of SVR encourage the treatment.
- Management of side-effects and social or life conditions of patients are important factors to consider before treatment.

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