New Microbiologica, **38**, 21-27, 2015

# Real life experience in treatment of HIV-1/HCV-coinfected patients with pegylated interferon alpha and ribavirin: predictors of SVR

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**SUMMARY**

Single nucleotide polymorphisms (SNPs) rs12979860 and rs8099917 near the interleukin 28B gene are predictors of virological response (SVR) to IFN-based therapy for monoinfected chronic hepatitis C patients. We retrospectively evaluated the impact of IL28B SNPs and other factors on SVR in a cohort of 102 HIV-1/HCV-coinfected patients treated with pegylated interferon-α (peg-INFα) and ribavirin. Data on baseline features and virological response at different time-points were collected.

Overall, 89/102 patients (87%) were males, 44 (43%) of whom infected with HCV genotype 1; SVR was achieved by 50 patients (49%). A univariate logistic regression analysis demonstrated that rs129679860 SNP genotype CC ($p<0.034$), rs8099917 SNP genotype TT ($p<0.01$), HCV genotype 2 or 3 ($p<0.0001$), low HCV viral load ($p<0.028$) and RVR (rapid virological response) ($p<0.0001$) were associated with a higher likelihood of SVR. Multivariate analysis confirmed only RVR and HCV genotype as independent predictors of SVR.

In a real life setting, the importance of RVR and IL28B SNPs was confirmed as predictive of SVR to identify patients with a higher likelihood of SVR to Peg-INFα+RBV, and also to designate a deferred therapy for patients with a low likelihood of SVR for whom it is preferable to wait for more successful options.

*KEY WORDS:* IL28B SNPs, Predictors of SVR, HIV-1/HCV coinfection, HCV genotype.

*Received* June 6, 2014 *Accepted* September 24, 2014

## INTRODUCTION

Globally, chronic hepatitis C virus (HCV) infection is found in about one-quarter of all human immunodeficiency virus (HIV)-infected individuals and is one of the leading causes of mortality and morbidity in these patients. Until recently, the combination of pegylated interferon alpha (peg-IFNα) and ribavirin (RBV) was the standard of care for treatment of chronic hepatitis C in HIV-HCV-coinfected patients, and it remains the only therapeutic approach for non-genotype 1 patients with chronic hepatitis C in Italy. However, the rate of sustained virological response (SVR) in HIV-1/HCV-coinfected patients treated with peg-IFNα/RBV is lower than that for HCV monoinfected individuals (Manns *et al.*, 2001; Fried *et al.*, 2002; Sulkowski *et al.*, 2008), with genotypes 1 or 4 showing the lowest likelihood of achieving SVR (14-38%), and genotype 2 or 3 presenting SVR rates up to 60% (Torriani *et al.*, 2004).

Many predictors of SVR with peg-IFNα/RBV are already known: HCV genotype, baseline HCV viral load, stage of liver fibrosis and rapid virological response (RVR; defined as clearance of HCV RNA by week 4). Moreover, the management of patients with HCV-related liver disease has been improved by the finding that single nucleotide polymorphisms (SNPs) rs12979860

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and rs8099917, located on chromosome 19 near the interleukin 28B (IL28B) gene, are associated with treatment response in HCV-monoinfected (Ge *et al.*, 2009; Suppiah *et al.*, 2009; Tanaka *et al.*, 2009) and HIV/HCV-coinfected patients. In fact, patients carrying a rs8099917 G allele and a rs12979860 T allele demonstrate a low probability of virological success (Pineda *et al.*, 2010; Rallon *et al.*, 2010; Neukam *et al.*, 2012).
Recently, the therapeutic anti-HCV armamentarium has been enlarged by the introduction of two NS3/4 protease inhibitors, Telaprevir and Boceprevir, which can be used for patients infected with HCV genotype 1. New therapeutic options, including other direct antiviral agents (DAAs) belonging to different drug classes, with or without IFN, and in some cases also active against genotypes other than 1, are on approval. However, some individuals, such as non-genotype 1 naïve and experienced patients with advanced fibrosis, require immediate treatment. Therefore, while waiting for new therapeutic opportunities, the knowledge of the most useful predictors of SVR can currently identify patients with the highest probability of SVR with a peg-IFNα plus RBV-based therapy.
This paper presents our experience of anti-HCV treatment with Peg-IFN and RBV of a cohort of HIV-1/HCV-coinfected patients from a single center. The aim of our study was to evaluate the impact of IL28B SNPs and other factors predictive of SVR in a cohort of HIV-1/HCV-coinfected patients treated in a "real life" setting.

## MATERIALS AND METHODS

This observational retrospective study analyzed the clinical records of 102 HIV-1/HCV-coinfected patients who received a treatment with peg-IFNα/RBV from January 2001 through May 2011 (Clinic of Infectious Diseases, University of Bari, Italy). Clinical data included: epidemiological data, risk factors for HIV and HCV acquisition, blood biochemical parameters, CD4+ cell count, plasma HIV-1 and HCV viral load, HCV genotype, abdominal ultrasound and type of therapy. The dosage of weekly injections of Peg-IFN α-2a or 2b, the daily oral dose of RBV, treatment duration and the stopping rules were established according to the guidelines in force at the time of treatment (Soriano *et al.*, 2004; Rockstroh *et al.*, 2008).

### Classification of response

Patients were classified as having a rapid virological response (RVR) if there was HCV RNA clearance by week 4 and achieving SVR if plasma HCV RNA was undetectable six months after stopping treatment. Patients who did not complete treatment were considered non-SVR.

### Fibrosis detection

Fibrosis was evaluated by a pre-treatment liver biopsy for 66 patients. In patients for whom liver biopsy was not available, the diagnosis of cirrhosis was based on pre-treatment abdominal ultrasound, clinical and laboratory criteria.

### Genotyping SNPs

DNA samples isolated from whole blood were genotyped for two sets of IL28B SNPs, rs12979860 and rs8099917, using a real-time polymerase chain reaction (PCR) in a Corbett Research Termocycler (Rotor Gene 3000A) by fluorescent probes (Nuclear Laser Medicine - Italy) according to the manufacturer's instructions. The assay discriminated the different genotypes: wild-type homozygote (C/C, T/T), heterozygote (C/T, T/G), replaced homozygote (T/T, G/G) for rs12979860 and rs8099917, respectively.

### Statistical methods

Quantitative variables were summarized as mean and standard deviation if distributed according to Gauss, and as median and range if not normally distributed. Independent samples were compared with the student t-test or Wilcoxon test, as appropriate. Qualitative variables were summarized as counts and percentages. The comparison between independent samples was performed by the Chi-square test. In the case of multiple comparisons among independent groups, the p-value was adjusted according to the number of the layers using the permutational method. In order to evaluate the effect of clinical characteristics on the response to therapy, a univariate logistic regression model was used. In the logistic multivariate model, covariates were included if significant with univariate analysis (p-value <0.05 statistically

significant value). Statistical analyses were performed using SAS software V9.3 for PC.

### Ethics

Our study did not require approval from the ethics committee according to Italian law since it was performed as an observational retrospective study in the context of normal clinical routine (art.1, Law 211/2003). However, all patients provided informed consent for the use of their data for research purposes. Blood samples were obtained as part of standard patient care; DNA samples and data were anonymous, according to the requirements established by the Italian Data protection Code (Law 196/2003).

## RESULTS

### Study population

The main clinical characteristics of the 102 patients enrolled in our study are summarized in Table 1. A total of 89 patients (87%) were male (median age 41 years), 71 of whom had a prior history of drug injections; 86 patients (84%) were receiving antiretroviral therapy and 67% had undetectable HIV-1 viral load (<50 copies/mL). The median CD4 cell count was 489 cells/µl; only five patients (4.9%) had a CD4 cell count <200 cells/µl. Most patients (98%) had high ALT levels (>40 UI/mL), 67% had HCV-RNA >600.000 IU/ml at baseline, and 16.7% had cirrhosis. In addition, 5 patients (5%) were also HBV-coinfected but all had an undetectable HBV DNA. The most frequent HCV genotypes were genotype 1 (43%) and genotype 3 (51%). IL-28B SNPs were available for 85 patients; the proportions of rs129679860 CC, CT and TT were: 45.9%, 42.3% and 11.8%, respectively. Likewise, the proportions of rs809991717 TT, GT and GG were 68.2%, 28.2% and 3.6%, respectively.

Of the 102 patients included in our study, 25 (24.5%) were non-responders to a previous anti-HCV treatment based on non-pegylated IFN, while the remaining subjects (75.5%) were naïve.

### Response to HCV therapy

Overall, 50/102 patients (49%) achieved SVR. Among the 52 patients who did not achieve SVR, 35 were classified as non-responders, 11 were relapsers and six ceased treatment because of adverse events.

Table 2 indicates the correlation between SVR and HCV-genotype, HCV viral load at baseline, IL28B genotype and RVR. Using univariate logistic regression, HCV genotypes 2 and 3 ($p < 0.0001$) and RVR ($p < 0.0001$, respectively) were strongly associated with SVR; as expected, patients chronically infected with HCV genotype 1 or 4 had lower SVR rates. An association between low baseline HCV viral load and therapeu-

TABLE 1 - *Baseline characteristics of the 102 HCV-HIV infected patients included in the study.*

| | |
|---|---|
| **Total no. of pts** | 102 |
| **Age, years, median (range)** | 41 (24-50) |
| **Sex, Male, no. (%)** | 89 (87.3) |
| **Risk factor for HIV-HCV, no (%)** | |
| - History of infection drug use | 71 (69.6) |
| - Other | 31 (30.4) |
| **CD4 cell count** | |
| - cells/µl, median (range) | 489.5 (60-1,408) |
| - <200/µl no. (%) | 5 (4.9) |
| **Patients with HIV-RNA < or >50 copies/ml, no. (%)** | |
| - <50 | 68 (66.7) |
| - ≥50 | 34 (33.3) |
| **Patients receiving ART, no/(%)** | 86 (84.3) |
| - 2 N(t)RTIs+ 1PI | 45 (52.3) |
| - 2 N(t)RTIs+ 1NNRTI | 22 (25.6) |
| - Other | 19 (22.1) |
| **HCV-related liver damage** | |
| - Chronic hepatitis, no. (%) | 85 (83.3) |
| - Cirrhosis, no (%) | 17 (16.7) |
| **HCV RNA IU/ml, median (range)** | 963,000 (6,800-7,700,000) |
| - <600,000 IU/ml | 36 (35.3) |
| - ≥600,000 IU/ml | 66 (64.7) |
| **HCV Genotypes** | |
| - 1 | 44 (43.1) |
| - 2 | 1 (1.0) |
| - 3 | 52 (51.0) |
| - 4 | 5 (4.9) |
| **Elevated ALT >40 IU/L, no. (%)** | 100 (98) |
| **IL-28 B (rs129679860 SNP), no. (%)** | 85 |
| - CC | 39 (45.9) |
| - CT | 36 (42.3) |
| - TT | 10 (11.8) |
| **IL-28 B (rs809991717 SNP), no. (%)** | 85 |
| - TT | 58 (68.2) |
| - TG | 24 (28.2) |
| - GG | 3 (3.6) |

ART= antiretroviral therapy; SNP= Single Nucleotide Polymorphism.

TABLE 2 - *Baseline and on-treatment predictors of SVR to Peg-IFN/RBV treatment in HCV-HIV infected patients by univariate logistic regression analysis.*

| | *Treatment Success N=50* | *Treatment Failure N=52* | *p* | *OR (CL 95%)* |
|---|---|---|---|---|
| **Age, years (median, I and III quartile)** | 40.5 (38.0-45.0) | 41.0 (38.0-44.0) | 0.434 | 0.972 (0.904-1.044) |
| **Gender, n (%)** | | | | |
| - Male | 41 (82.00) | 48 (92.31) | 0.129 | 0.380 (0.109-1.325) |
| - Female | 9 (18.00) | 4 (7.69) | | Ref. |
| **CD4+ cell count, n (%)** | | | 0.617 | |
| - <200 | 3 (6.00) | 2 (3.85) | | 1.596 (0.255-9.977) |
| - ≥200 | 47 (94.00) | 50 (96.15) | | Ref. |
| **HCV genotypes, n (%)** | | | | |
| - 2 or 3 | 39 (78.00) | 14 (26.92) | **<0.0001** | **9.623 (3.884-23.843)** |
| - 1 or 4 | 11 (22.00) | 38 (73.08) | | Ref. |
| **ALT (IU/L) (median, I and III quartile)** | 129.5 (88.0-204.0) | 134.5 (74.0-200.5) | 0.406 | 1.002 (0.998-1.006) |
| **Fibrosis stage (66 tested patients) n (%)** | | | | |
| - 1 | 17 (53.1) | 13 (38.2) | 0.669 | 1.263 (0.434-3.671) |
| - 2 | 5 (15.6) | 12 (35.3) | | Ref. |
| - 3 | 7 (21.9) | 7 (20.6) | | |
| - 4 | 3 (9.4) | 2 (5.9) | | |
| **HCV RNA, n (%)** | | | | |
| - <600,000 IU/ml | 23 (46.00) | 13 (25.00) | **0.028** | **2.555 (1.105-5.911)** |
| - ≥600,000 IU/ml | 27 (54.00) | 39 (75.00) | | Ref. |
| **HCV-related liver damage** | | | | |
| **- Chronic hepatitis, n (%)** | 42 (84.00) | 43 (82.69) | 0.860 | 1.099 (0.387-3.118) |
| - Cirrhosis, n (%) | 8 (16.00) | 9 (17.31) | | Ref. |
| **IL28B rs 129679860 (85 tested patients)** | | | | |
| - CC, n (%) | 26 (56.52) | 13 (33.33) | **0.034** | **2.600 (1.073-6.299)** |
| - Non-CC, n (%) | 20 (43.48) | 26 (66.67) | | Ref. |
| **IL28B rs809991717 (85 tested patients)** | | | | |
| - TT, n (%) | 37 (80.43) | 21 (53.85) | **0.010** | **3.523 (1.345-9.228)** |
| - Non-TT, n (%) | 9 (19.57) | 18 (46.15) | | Ref. |
| **RVR (83 tested patients)** | | | | |
| - yes | 26 (66.67) | 7 (15.91) | **<0.0001** | **10.571 (3.711-30.113)** |
| - no | 13 (33.33) | 37 (84.09) | | Ref. |

tic success (p>0.028) was also obserWWWved. Moreover, the correlation was investigated between rs129679860 and rs809991717 IL28 genotypes and the likelihood of therapeutic success (Table 2). About 67% of the rs129679860 non-CC carriers failed treatment (p<0.034), while 80% of patients carrying TT rs809991717 genotype achieved SVR when compared to 20% of the rs809991717 non-TT allele carriers (p<0.01). When the association of rs129679860 and rs809991717 SNPs with therapeutic success according to HCV genotype was analyzed (as shown in Tables 3 and 4), the influence of the two SNPs on achievement of SVR was demonstrated only for individuals infected with HCV genotypes 1 and 4. In fact, among patients infected with "difficult to treat" HCV genotypes, the T allele of rs129679860 SNP (p<0.024) and the G allele of rs809991717 SNP (p<0.043) were associated with treatment failure. Conversely, HCV genotypes 2 or 3 were independently related to treatment success, irrespective of rs129679860 and rs809991717 SNPs.

TABLE 3 - *Association of rs129679860 SNP with SVR to Peg-IFN+RBV therapy according to HCV genotype.*

| | *Treatment success SVR N= 46* | | *Treatment Failure N=39* | | *p value* | *OR (CL 95%)* |
|---|---|---|---|---|---|---|
| **HCV genotype** | **CC** N=26 (56.5%) | **CT or TT** N=20 (43.5%) | **CC** N=13 (33.3%) | **CT or TT** N=26 (66.7%) | | |
| **1 or 4** N=39 (45.9%) | 7 (70.0%) | 3 (30.0%) | 8 (27.6%) | 21 (72.4%) | **0.024** | **6.125 (1.263-29.696)** |
| **2 or 3** N=46 (54.1%) | 19 (52.8%) | 17 (47.2%) | 5 (50.0%) | 5 (50.0%) | 0.876 | 1.118 (0.275-4.540) |

TABLE 4 - *Association of rs809991717 SNP with SVR to Peg-IFN+RBV therapy according to HCV genotype.*

| | *Treatment success SVR N= 46* | | *Treatment Failure N=39* | | *p value* | *OR (CL 95%)* |
|---|---|---|---|---|---|---|
| **HCV genotype** | **TT** N=26 (56.5%) | **TG or GG** N=20 (43.5%) | **TT** N=13 (33.3%) | **TG or GG** N=26 (66.7%) | | |
| **1 or 4** N=39 (45.9%) | 9 (90.0%) | 1 (10.0%) | 14 (48.3%) | 15 (51.7%) | **0.043** | **9.643 (1.079-86.210)** |
| **2 or 3** N=46 (54.1%) | 28 (77.8%) | 8 (22.2%) | 7 (70.0%) | 3 (30.0%) | 0.611 | 1.500 (0.314-7.169) |

A multivariate logistic analysis was performed which included only the variables significantly associated with treatment response at univariate analysis. Using a stepwise method for selection covariates, the covariate rs809991717 SNP, rs129679860 SNP and HCV viral load were excluded because they lost their significance, whereas RVR (OR=7.119; CL 2.314-21.901; p=0.001), and HCV genotype (OR=5.726; CL 1.936-16.930; p=0.002), continued to be significant predictors of SVR.

## DISCUSSION

HIV-HCV coinfection is one of the most important causes of mortality and morbidity in HIV-HCV-coinfected patients and represents a very serious global health issue for these patients. The natural course of liver disease differs in HIV-HCV-coinfected patients compared to HCV monoinfected patients. In HIV patients with concomitant HCV chronic hepatitis, the rate of severe liver fibrosis is higher and liver failure and HCV-related mortality events are more frequent (Sulkowski *et al*., 2002; Pineda *et al*., 2007; Lin *et al*., 2013). As a consequence, hospitalization costs are also higher for these patients (De Luca *et al.*, 2002). Conversely, a successful anti-HCV treatment which reduces progression of liver fibrosis also diminishes liver-related and overall mortality in HIV-infected patients (Pineda *et al*., 2007).

Currently, the NS3/4 protease inhibitors Telaprevir and Boceprevir are available for patients infected with HCV genotype 1. When these new drugs are used in association with peg-IFN/RBV the likelihood of achieving SVR is increased. HIV-HCV-coinfected patients treated with either Boceprevir or Telaprevir had a 61% and 74% SVR rate, respectively, compared to those treated with peg-IFN-a/RBV alone (Sulkowski *et al*., 2013[a]; Sulkowski *et al*., 2013[b]; Rockstroh *et al*., 2013). New therapeutic options, including other direct antiviral agents pertaining to different drug classes with or without IFN and in some cases also active against genotypes other than 1, are on approval. However, it is impossible to predict when they will become commercially available worldwide, and it is expected that they will have higher costs. In addition, Peg-IFN-a and RBV remain the standard for care of non-genotype 1 naïve or experienced coinfected patients, especially those with advanced fibrosis. Therefore, knowledge of the most useful SVR predictors is very important to identify patients with the highest probability of SVR with Peg-IFN-a and RBV.

In the past, predictors of response to anti-HCV therapy were extensively studied in HCV-monoinfected patients whereas only few studies, especially outside clinical trials, have

been performed in patients with HIV-HCV coinfection, a population which is difficult to treat and has extremely lower response rates.

In our experience, about 50% of HIV-1/HCV-coinfected patients treated with Peg-IFN/RBV achieved a SVR. When variables associated with the probability of success were analyzed, a strong association between HCV genotype ($p<0.0001$), HCV viral load ($p<0.028$), RVR ($p<0.0001$), rs129679860 SNP genotype CC ($p<0.034$) and rs809991717 SNP genotype TT ($p<0.01$) was found. However, even if both polymorphisms have been shown to be valid predictors of SVR with univariate analysis, they lost their statistical significance with multivariate analysis.

Which SNP represents the most useful predictor of response to anti-HCV treatment is still controversial (Aparicio *et al.*, 2010; De Castellarnau *et al.*, 2012). Recently, new SNPs which might be associated with response to treatment have been described: Franco *et al*. (2013) suggested that the ss469415590 genotype is a better predictor of treatment failure than IFNL3 (Interferon λ 3) rs12979860. We maintain that a combined effect of all these genetic variables intervenes to determine the response to treatment.

Lastly, some authors have reported a possible correlation between CD4 count in HIV-1/HCV-coinfected patients and SVR. Two studies (Valerio *et al.*, 2008; Mira *et al.*, 2009) reported that the efficacy of pegylated IFN plus RBV among subjects with low CD4 count was similar to that found in subjects without severe immunodeficiency. Our study disclosed no significant differences between patients with or without SVR in terms of gender, age, liver enzyme levels and baseline CD4 count. Our results might have been influenced by certain characteristics of our population including only a limited number of females and patients with CD4 count <200 cells/μl, in addition to the fact that the age of the patients (38-45 years) was young and high ALT levels at baseline were seen in 98% of patients.

We are aware that this study has certain limitations, including its retrospective nature and the limited number of patients. In addition, IL28 genotype and pre-treatment liver biopsies were not available for all patients.

In conclusion, in a real life setting we confirmed the importance of RVR and IL28B SNPs as predictors of SVR to a therapy based on peg-IFNα and RBV. This knowledge is still useful for identifying non-genotype 1 naïve and experienced patients with advanced fibrosis with a higher likelihood of SVR and conversely, for deferring therapy in patients with a low likelihood of virological success, for whom it is preferable to wait for more successful options.

*ACKNOWLEDGEMENT*

*We thank Mrs Paulene Butts who provided medical writing services on behalf of the University of Bari, Italy.*

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