Research Article

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# Identification of naïve HCV-1 patients with chronic hepatitis who may benefit from dual therapy with peg-interferon and ribavirin

Angelo Andriulli[1,*], Vito Di Marco[2], Maurizio Margaglione[3], Antonio Massimo Ippolito[1], Giovanna Fattovich[4], Antonina Smedile[5], Maria Rosa Valvano[1], Vincenza Calvaruso[2], Domenica Gioffreda[1], Michele Milella[6], Filomena Morisco[7], Martina Felder[8], Giuseppina Brancaccio[9], Massimo Fasano[10], Pietro Gatti[11], Paolo Tundo[12], Michele Barone[13], Raffaele Cozzolongo[14], Mario Angelico[15], Giovanna D'Andrea[3], Nicola Andriulli[16], Maria Lorena Abate[5], Giuseppe Mazzella[17], Giovanni Battista Gaeta[9], Antonio Craxi[2], Teresa Santantonio[10]

[1]*Division of Gastroenterology, Casa Sollievo Sofferenza Hospital, IRCCS, San Giovanni Rotondo, Italy;* [2]*Clinic of Gastroenterology, University of Palermo, Italy;* [3]*Department of Clinical and Experimental Medicine, University of Foggia, Italy;* [4]*Clinic of Gastroenterology, Department of Medicine, University of Verona, Italy;* [5]*Department of Medical Sciences, University of Torino and Department of Gastroenterology and Hepatology, Azienda Ospedaliera Città della Salute e della Scienza, Torino, Italy;* [6]*Clinic of Infectious Diseases, University of Bari, Italy;* [7]*Gastroenterology, Department of Clinical Medicine and Surgery, Federico II University of Napoli, Italy;* [8]*Division of Gastroenterology, Central Hospital, Bolzano, Italy;* [9]*Infectious Diseases, Second University of Napoli, Italy;* [10]*Clinic of Infectious Diseases, University of Foggia, Italy;* [11]*DIMO Medical Oncology, University of Bari, Italy;* [12]*Division of Infectious Diseases, S. Caterina Novella Hospital, Galatina, Italy;* [13]*Division of Gastroenterology, University of Bari, Italy;* [14]*Division of Gastroenterology, "S. de Bellis" Hospital, IRCCS, Castellana Grotte, Italy;* [15]*Hepatology and Liver Transplantation Unit, Tor Vergata University, Roma, Italy;* [16]*Department of Chemical Pharmaceutics, University La Sapienza, Rome, Italy;* [17]*Division of Gastroenterology, University of Bologna, Italy*

**Background & Aims**: The pool of HCV genotype 1 patients likely to be cured by peg-interferon and ribavirin remains to be quantified.

**Methods**: In 1045 patients treated with peg-interferon and ribavirin, two therapeutic strategies were confronted: the first one evaluated only baseline variables associated with sustained virological response (SVR), and the second one included the rapid virologic response (RVR) in addition to baseline predictors. An 80% SVR rate was the threshold to retain a strategy as clinically relevant.

**Results**: Overall, 414 patients (39.6%) attained SVR. In the first strategy, the hierarchy of features independently associated with SVR was *IL28B* CC genotype (OR 5.082; CI 3.637–7.101), low (<400,000 IU) viremia (OR 2.907; CI 2.111–4.004), F0–F2 fibrosis (OR 1.631; CI 1.122–2.372) and type 2 diabetes (OR 0.528; CI 0.286–0.972). In the alternative strategy, SVR was associated with RVR (OR 6.273; CI 4.274–9.208), *IL28B* CC genotype (OR 3.306; CI 2.301–4.751), low viremia (OR 2.175; CI 1.542–3.070), and F0–F2 fibrosis (OR 1.506; CI 1.012–2.242). Combining the favorable baseline variables, the rates of SVR ranged from 42.4% to 83.3%, but only 66 patients (6.3%, overall) with all predictors could be anticipated to reach the >80% SVR threshold. Only 26.6% of no-RVR patients attained SVR. Among the 255 RVR patients, the likelihood of SVR was 61.8% in those with unfavorable predictors, 80% in the presence of a single predictor, and 100% when both predictors were present. By using this model, 200 patients (19.1%) were predicted to have an 80% chance of being cured with dual therapy.

**Conclusions**: A consistent subset of naïve HCV-1 patients, identified by some baseline characteristics and RVR, may benefit from dual treatment with peg-interferon and ribavirin.



Keywords: HCV; Chronic HCV liver disease; Peg-interferon; Ribavirin; Predictors of response.

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* Corresponding author. Address: Division of Gastroenterology, Casa Sollievo Sofferenza Hospital, IRCCS, viale Cappuccini 1, San Giovanni Rotondo, Italy. Tel.: +39 0882 410263; fax: +39 0882 835411.

*E-mail address:* a.andriulli@operapadrepio.it (A. Andriulli).

## Introduction

There have been significant changes in the management of patients with HCV genotype 1 (HCV-1) infection since the approval of the two HCV NS3/4A serine protease inhibitors (PIs), telaprevir and boceprevir, by regulatory agencies. The addition of PIs to the previous standard of care, Peg-interferon (PegIFN) and ribavirin (RBV), has boosted the sustained virologic response (SVR) to approximately 75% in treatment-naïve patients [1,2]. Echoing these results, scientific communities [3,4] and governmental health care organizations [5] recommended triple

therapies with PegIFN, RBV, and PIs as the new standard of care for genotype 1 untreated and previously treated patients. The therapeutic advances with triple therapies came at the expenses of increased adverse effects, significant drug-drug interactions, and induction of viral mutations. In addition, despite positive cost-effective analyses [6,7] and better outcomes than dual therapy, the use of triple therapy is associated with increased costs, which may threaten to maintain a disparity in access to care. Especially for countries with significant disease burden of HCV infection and real budgetary and resource constraints, the expense of these new regimens may make the interferon regimens more reasonable.

Despite the gain in SVR rates provided by triple therapies, it remains that conventional dual therapies may achieve SVR in 40–50% of naïve patients with HCV-1 infection [8]. The ability to identify patients likely to achieve high SVR rates following dual therapies appears clinically valuable and appropriate for short-term budgeting. Several virus and patient features, such as serum HCV RNA levels and the degree of fibrosis, markedly affect the likelihood of attaining an SVR, whereas other influential factors with lesser impact include age, gender, race, and body weight/body mass index [9,10]. Recent data have further highlighted that the favorable *IL28B* polymorphism rs12979860 [11] and/or the achievement of rapid virologic response (RVR) [12] may identify patients who stand to benefit the most from PegIFN and RBV. By adopting baseline predictors of SVR as a criterion to allocate treatment-naïve patients to dual or triple therapies, it could be possible to initiate conventional regimens in those with favorable predictors, and to offer *ab initio* triple therapy to those less likely to benefit from standard therapy and for whom the increased risk of side-effects and the increased cost of drugs may be most justified. The alternative strategy would be to test all candidates to therapy for interferon sensitivity at week 4 from starting dual therapy, and add on PIs only to those with poor responsiveness. The magnitude of the pool of patients who need to be allocated to dual or triple therapies remains to be exactly quantified.

Objective of this large, non-interventional cohort study on genotype 1 chronic HCV infection was to provide a realistic estimate of the proportion of patients who might benefit from dual antiviral therapy. To accomplish this, we considered two alternative strategies for allocating treatment: the first one reserving PegIFN and RBV to the subset of patients with favorable predictors of SVR at baseline, and the second one restricting this regimen to those with interferon sensitivity, as ascertained by negative HCV viremia at week 4 from the start of therapy. As PIs-based triple therapy has boosted SVR rates to approximately 75% [1,2], a strategy that still contemplates the option of dual therapy for HCV-1 previously untreated patients had to guarantee for an SVR rate of >80% to be considered as clinically relevant.

## Materials and methods

### *Patients*

Current retrospective analysis refers to HCV-1 patients treated with PegIFN and RBV at 15 Italian centers from 2005 to 2010. The database at each participating institution was interrogated for patients who were naïve to antiviral treatment, and presented with an initial diagnosis of chronic hepatitis or compensated liver cirrhosis. For this analysis, HBV and HIV co-infected patients were excluded.

Of the 2359 HCV-1 infected patients deposited into the databases, 1045 individuals (44,3%) were retained in the final analysis. We excluded by protocol patients who withdrew treatment by week 24 due to intolerance or severe side effects (n = 195), those non consenting to *IL28B* genotyping (n = 365), those lost to follow-up (n = 294), those who had died (n = 82), and those with missing viremia results at week 4 of therapy (n = 213), or with missing histologic or FibroScan® evaluation (n = 165) (Fig. 1). Patients received either PegIFNα-2b or α-2a plus ribavirin. To comply with treatment guidelines, patients with negative HCV RNA at week 12 continued treatment for 48 weeks, whereas therapy was halted at week 24 in those with persistent viremia. Patients with low serum HCV RNA levels (lower than 400,000 IU/ml) at baseline who achieved an RVR had to stop therapy at week 24. At the time of the recall visit, information about the latest HCV RNA testing, liver chemistry, and abdominal ultrasound was recorded. The study was approved by ethics committees, and conducted according to provisions of the Declaration of Helsinki and Good Clinical Practice Guidelines.

### *Genotyping of IL28B rs12979860 polymorphism*

*IL28B* rs12979860 SNP was genotyped using the TaqMan SNP genotyping kit (ABI ABI TaqMan) and the ABI 7900HT sequence detection System (Applied Biosystems, Foster City, CA, USA).

### *Viral load and HCV genotyping*

HCV genotyping was performed by the commercially available Inno-LiPA assay (Innogenetics, Zwijndrecht, Belgium). Serum HCV RNA was quantified at baseline by reverse transcription-PCR, using the Cobas Amplicor HCV Monitor Test, v 2.0 (Roche, Basel, Switzerland). Qualitative HCV RNA assessment was made at weeks 4, 24, and 48 during treatment, and at week 24 after stopping therapy. Rapid virologic response (RVR) was defined as undetectable HCV RNA in serum at week 4 of therapy, and SVR as undetectable HCV RNA in serum 24 weeks after stopping therapy.

### *Assessing the degree of hepatic fibrosis*

Histologic data were available for 660 patients who consented to liver biopsy, and classified by local pathologists according to different scoring systems, which were then converted to uniform criteria as the Metavir score [13]. In the remaining patients, cirrhosis was diagnosed on the occurrence of one or more following criteria: a liver elastometric (FibroScan®) value $\geqslant$13kPa, and/or oesophageal varices at endoscopy, and/or platelet count <100,000/ml [14,15]. To ascertain the presence of F3 fibrosis, the following criteria were followed: a FibroScan® value <13 but $\geqslant$9 kPa, and/or platelet count >100,000 but <140,000/ml [16–17].

### *Statistical analysis*

All data were analyzed on the intention to treat basis using SPSS 13.0 for Windows software (SPSS Inc., Chicago, IL. USA). Differences between continuous variables, expressed as medians and Interquartile Ranges (IQR), were analyzed using non-parametric Mann-Whitney Test, whereas Chi-square and Fisher's exact test were used for categorical variables. The association between baseline features and SVR was calculated using multiple logistic regression analysis. The first model was stratified by a set of cohort characteristics at baseline, including age (<*vs.* $\geqslant$50 years), gender, BMI, serum alanine aminotransferase (ALT) levels, liver fibrosis stage (F0–F2 *vs.* F3–F4), HCV genotype (1a *vs.* 1b), baseline viral load (<*vs.* $\geqslant$400,000 IU/ml) [18], *IL28B* genotypes (CC *vs.* CT/TT), the occurrence of diabetes, and the type of PegIFN (alpha-2a *vs.* alpha 2b). The second model incorporated RVR along with baseline variables. Variables with a threshold value of $p$ <0.10 at univariate analysis were included in the models, and only variables with a threshold value of $p$ <0.05 were retained in the final model. The results were expressed as odds ratios (OR) with corresponding 95% Confidence Interval (CI). Finally, patients were sub-grouped according to the previously identified predictors in order to select the ones with a >80% likelihood of attaining SVR following PegIFN and RBV.

## Results

### *Patient characteristics (Table 1)*

A total of 1045 Caucasian patients were recruited for the study. A majority of patients were males (57.4%), older than 50 years (63.2%), infected by HCV-1 subtype 1b (86%), and

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with high (⩾400,000 IU/ml) viral load (68.4%). As to the *IL28B* polymorphisms, 277 (26.5%) patients were homozygous for the CC allele, 548 (52.4%) heterozygous for CT, and 220 (21.1%) homozygous for TT. PegIFN alpha-2a was administered to 61.9% of the patients, and PegIFN alpha-2b to the remaining individuals. RBV was given at a mean dosage of 14 ± 2 mg/kg of body weight.

*Efficacy of treatment and factors associated with SVR (Table 1)*

By intention-to-treat analysis, 414 patients (39.6%) attained an SVR. Among the 255 patients (24.4%) who achieved RVR, 204 individuals cleared the virus following therapy (80%).

At univariate analysis, age (dichotomized at 50 years), blood glucose values, platelet counts, serum HCV RNA levels (dichotomized at 400,000 UI/ml), genotypes of the rs12979860 SNP (CC *vs.* CT/TT) and staging of fibrosis (F0/F2 *vs.* F3/F4) were significantly associated with SVR ($p$ <0.05) (Table 1). We analyzed the treatment duration in patients with low HCV RNA levels at baseline. Among 123 patients who achieved RVR and had baseline serum HCV-RNA levels <400,000 IU/ml, 33 individuals were treated for 24 weeks and 27 of them (82%) achieved an SVR; of the remaining 90 patients treated for 48 weeks, 81 subjects (90%) eventually cleared the infection.

At multivariate analysis (Table 2), the hierarchy of baseline factors independently associated with SVR (model A) were the CC genotype of the *IL28B* locus (OR 5.082; CI 3.637–7.101), serum HCV-RNA levels <400,000 IU/ml (OR 2.907; CI 2.111–4.004), F0–F2 fibrosis (OR 1.631; CI 1.122–2.372) and type 2 diabetes (OR 0.528; CI 0.286–0.972). When the RVR status was included among predictors of SVR (model B), the hierarchy of factors independently associated with SVR at multivariate analysis was RVR (OR 6.273; CI 4.274–9.208), CC genotype of the *IL28B* locus (OR 3.306; CI 2.301–4.751) serum HCV-RNA levels <400,000 IU/ml (OR 2.175; CI 1.542–3.070) and F0–F2 fibrosis (OR 1.506; CI 1.012–2.242).

**Table 1. Univariate analysis of baseline feature and rapid virological response associated with sustained virological response (SVR) in 1045 patients.**

| Variables | Overall n = 1045 | No SVR n = 631 (60.4%) | SVR n = 414 (39.6%) | Univariate analysis *p* value |
|---|---|---|---|---|
| Sex (No., %) | | | | |
| Male | 600 (57.4) | 374 ( 62.3) | 226 (37.7) | 0.134 |
| Female | 445 (42.6) | 257 (57.8) | 188 (42.2) | |
| Age (No., %) | | | | |
| <50 yr | 383 (36.7) | 200 (52.2) | 183 (47.8) | <0.001 |
| ≥50 yr | 662 (63.2) | 431 (65.1) | 231 (34.9) | |
| Body mass index (kg/m$^2$)~ | 25 (23-28) | 26 (23-28) | 25 (22-27) | 0.012 |
| ALT (ULN)~ | 2 (1-3) | 2 (1.3-3) | 1.98 (1.15-3) | 0.263 |
| Platelet count (x10$^3$/mm$^3$)~ | 200 (151-235) | 199 (144-235) | 205 (168-237) | 0.002 |
| Liver fibrosis (No., %) | | | | |
| Stage F0-F2 | 664 (63.5) | 365 (55.0) | 299 (45.0) | <0.001 |
| Stage F3-F4 | 381 (36.5) | 266 (69.8) | 115 (30.2) | |
| Type 2 diabetes (No., %) | | | | |
| Yes | 110 (10.5) | 80 (72.7) | 30 (27.3) | 0.005 |
| No | 935 (89.5) | 551 (58.9) | 384 (41.1) | |
| HCV genotypes* (No., %) | | | | |
| 1a | 144 (14.0) | 79 (54.9) | 65 (45.1) | 0.154 |
| 1b | 885 (86.0) | 541 (61.1) | 344 (38.9) | |
| Serum HCV RNA levels (No., %) | | | | |
| <400.000 IU/ml | 330 (31.6) | 151 (45.8) | 179 (54.2) | <0.001 |
| ≥400.000 IU/ml | 715 (68.4) | 480 (67.1) | 235 (32.9) | |
| *IL28B* rs12979860 SNP (No., %) | | | | |
| CC | 277 (26.5) | 93 (33.6) | 184 (66.4) | <0.001 |
| CT | 548 (52.4) | 384 (70.1) | 164 (29.9) | |
| TT | 220 (21.1) | 154 (70.0) | 66 (30.0) | |
| Type of PegIFN (No., %) | | | | |
| PegIFN-α2a | 647 (61.9) | 394 (60.9) | 253 (39.1) | 0.665 |
| PegIFN-α2b | 398 (38.1) | 237 (59.5) | 161 (40.5) | |
| RVR | 255 (24.4) | 51 (20.0) | 204 (80.0) | <0.001 |
| no RVR | 790 (75.6) | 580 (73.4) | 210 (26.6) | |

* Undifferentiated subtype (n = 16).
~ (Median, IQR).

**Table 2. Multivariate analysis of baseline feature (Model A) and baseline feature and rapid virological response (Model B) associated with sustained virological response (SVR) in 1045 patients.**

| Variables | Multivariate analysis | | | |
|---|---|---|---|---|
| | Model A | | Model B | |
| | OR (95% CI) | *p* value | OR (95% CI) | *p* value |
| Age <50 yr | 1.35 (0.991-1.833) | 0.06 | 1.33 (0.960-1.851) | 0.086 |
| Body mass index | 0.98 (0.946-1.016) | 0.27 | 0.98 (0.940-1.014) | 0.214 |
| Platelet count | 1.00 (0.998-1.003) | 0.65 | 1.00 (0.998-1.003) | 0.819 |
| Liver fibrosis (F0-F2) | 1.63 (1.122-2.372) | 0.01 | 1.51 (1.012-2.242) | 0.043 |
| Type 2 diabetes | 0.53 (0.286-0.972) | 0.04 | 0.58 (0.306-1.115) | 0.103 |
| Serum HCV RNA levels (<400.000 IU/ml) | 2.91 (2.111-4.004) | <0.001 | 2.17 (1.542-3.070) | <0.001 |
| *IL28B* rs12979860 (CC) | 5.08 (3.637-7.101) | <0.001 | 3.31 (2.301-4.751) | <0.001 |
| RVR | - | - | 6.27 (4.274-9.208) | <0.001 |

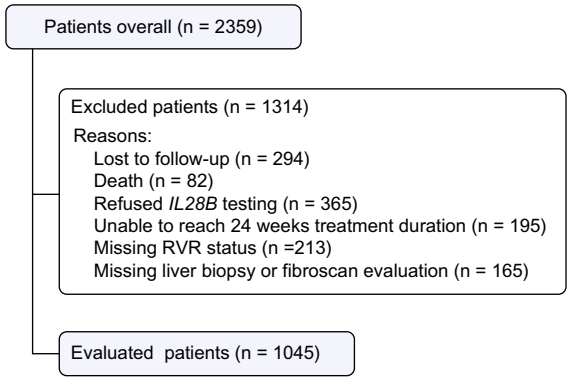


**Fig. 1. Flow of patients enrolled into the study.**

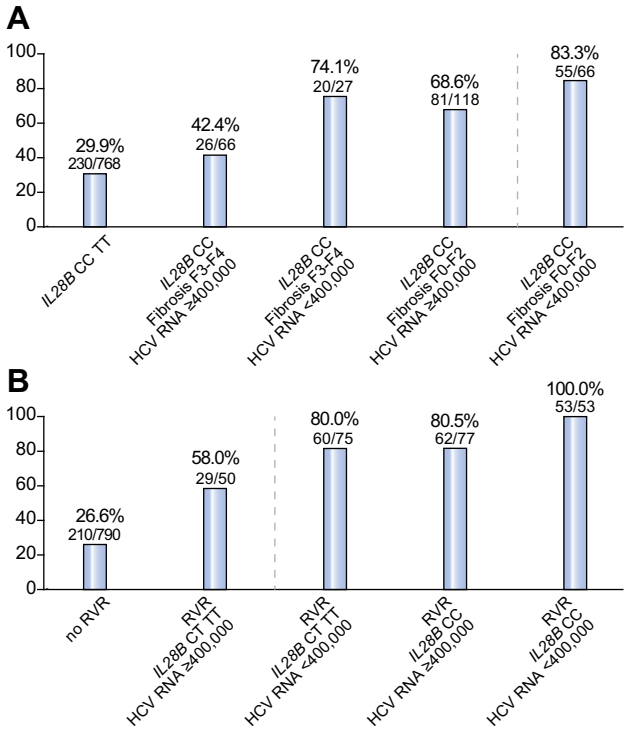


**Fig. 2. Sustained virologic response rates following PegIFN/RBV in 1045 HCV genotype 1 patients.** (A) Stratified according to independent predictors for SVR at baseline; (B) stratified according to baseline predictors and on-treatment virologic response. *IL28B* CC or TT or CT = *IL28B* polymorphism rs12979860. RVR, rapid virologic response.

*Estimating the pool of patients who could achieve SVR following dual therapy*

By using data from model A (Fig. 2A), 768 patients with CT or TT genotype at the rs12979860 SNP had a 29.9% likelihood of achieving SVR. By combining independent baseline features associated with SVR, the probability of achieving SVR ranged from 42.4% to 83.3%. In patients carrying the CC genotype, the SVR rate was 42.4% when the other two unfavourable predictors (i.e., F3–F4 fibrosis and serum HCV-RNA levels $\geqslant$400,000 IU/ml) were concomitantly present, and increased to values of 74.1% and 68.6%, when a single favourable predictor was detected. Only in the subset of patients displaying all three favourable factors (CC genotype, F0–F2 fibrosis, and serum HCV-RNA levels <400,000 IU/ml) the SVR rate was clinically relevant (83.3%), but this condition was present in only 55 out of the total 1045 HCV-1 patients, a marginal proportion of 5.3%.

When we incorporated the RVR status (model B) to baseline predictors, the prediction power for SVR among different subgroups of patients increased substantially (Fig. 2B). Only 26.6% of patients without RVR attained SVR, whereas among the 255 RVR patients, the likelihood of SVR was 68.0% in patients with concomitant unfavorable predictors (no-CC genotype and high viremia), but did attain the clinically significant threshold of 80% when one positive predictor happened to be present. Whenever RVR carriers of the CC genotype presented with low viremia, 100% of them cleared HCV following dual therapy. By using this model, 200 of the entire cohort of 1045 patients (19.1%) could be predicted at week 4 of therapy to have an 80% chance of being cured with dual therapy.

*Stratifying RVR patients by hepatic fibrosis*

Even if the prediction power of hepatic fibrosis was inferior to the other factors, we evaluated the influence of the stage of hepatic fibrosis on SVR in our 255 patients who cleared the HCV at

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**Table 3. Sustained virological response (SVR) rates following peg-interferon and ribavirin in 255 genotype 1 patients with rapid (week 4) virologic response, stratified according to the stage of liver fibrosis.**

| RVR n = 255 | | | | | |
|---|---|---|---|---|---|
| | | Total | | SVR | |
| | | n | % | n | % |
| **F0-F2** | | | | | |
| n = 186 | CC + low viremia | 42 | 22.6 | 42 | 100.0 |
| | CC + high viremia | 55 | 29.6 | 47 | 85.5 |
| | no CC + low viremia | 53 | 28.5 | 42 | 79.2 |
| | no CC + high viremia | 36 | 19.3 | 20 | 55.6 |
| **F3-F4** | | | | | |
| n = 69 | CC + low viremia | 11 | 15.9 | 11 | 100.0 |
| | CC + high viremia | 22 | 31.9 | 15 | 68.2 |
| | no CC + low viremia | 17 | 24.6 | 13 | 76.5 |
| | no CC + high viremia | 19 | 27.6 | 14 | 73.7 |

treatment week 4 (Table 3). In the 186 patients with absent/moderate fibrosis (F0–F2), SVR rates were optimal (>80%) in those presenting with a single or two positive predictors of SVR, but were suboptimal (55.6%) in those with *IL28B* CT/TT genotypes and high viremia. Among the 69 RVR patients with advanced fibrosis/cirrhosis, SVR rates were high only in cases with low viremia.

## Discussion

When considering therapy for patients chronically infected by HCV genotype 1, finding the optimal balance between managing therapy-related adverse effects and costs, as well as optimizing the chance of SVR after conventional or new antiviral therapies are major challenges. Because the new antiviral regimens still involve PegIFN [1,2], the likelihood of success will continue to rely on the interferon responsiveness. In this large cohort of 1045 patients, we have shown that on-treatment virologic response, specifically the HCV RNA undetectability at week 4, was dominant over all other variables at determining the likelihood of SVR following PegIFN and ribavirin.

In our population, an RVR was achieved by 255 (24.4%) patients, and 204 of them (80%) attained SVR. At multivariate analysis (Table 2), the prediction ability of RVR for an SVR was about 2-fold higher than that of the CC genotype of *IL28B*, and about 3-fold stronger than that of low viremia. The low predictive power of *IL28B* genotyping for SVR in our series of Caucasian patients with chronic HCV infection deserves a comment. Of the 277 patients homozygous for the CC allele, only 47% and 66% were capable of attaining RVR and SVR, respectively, after conventional dual therapy. In addition, of 70 no-CC genotype patients with RVR and low viremia, 55 individuals (78.6%, Fig. 2B) experienced SVR. Similar to reports from Thompson *et al.* [19] and Di Marco *et al.* [20], the weak utility of the *IL28B* genotype for predicting an optimal treatment outcome, once RVR was determined, could suggest that the major effect of the *IL28B* polymorphism was to influence viral kinetics within the initial months of therapy. As a matter of fact, among our patients with RVR more than 80% eventually cleared the infection following conventional dual therapy, the only exception being those with no-CC genotype and high viremia (Fig. 2B).

In addition, our data provide potentially valuable information on how to predict the likelihood of SVR, and which patients to prioritize for treatment with triple therapies. As to the first issue, none of the pretreatment factors, namely the *IL28B* genotype, the viral load, and the fibrosis stage, accurately predicted response to therapy for an individual patient. Indeed, individuals with poor predictors may still respond to therapy, as it was the case for 29.9% of our 768 patients carrying the *IL28B* gene CT or TT types, 30.2% of 381 patients with advanced fibrosis, and 32.9% of 715 patients with high viremia. Consequently, in the clinical assessment of an individual patient, neither carriage of "poor-prognosis" *IL28B* rs12979860 genotypes nor high viral load or significant hepatic fibrosis would preclude the chance of SVR. In the present study, by relying on the three identified independent predictors for SVR (i.e., *IL28B* CC type, low viremia, and F0–F2 fibrosis), only 66 individuals (6.3% overall) could have been identified before starting therapy as having a high (>80%) chance of SVR following conventional dual therapy. On the contrary, by considering the RVR status, 200 patients (19.1%, overall) would be deemed at high likelihood of SVR following PegIFN and RBV. This observation suggests that it does not matter, which baseline feature HCV-infected patients present with, but rather how they achieve early undetectable HCV RNA. Actual on-treatment viral responses provide the clinical trump card of response prediction for PegIFN and RBV regimens: as long as patients continue treatment with dual therapy after reaching this virological landmark, they are at high likelihood of achieving an SVR.

The degree of hepatic fibrosis is one of the currently followed criteria to tailor treatment success and duration in the HCV genotype 1 [9,10]. However, in the present investigation, this characteristic was picked up at multivariate analysis as having an independent prediction power for SVR when only baseline features were evaluated in Model A. However, the negative influence of advanced fibrosis on SVR rates was obscured in our cohort of patients when the RVR status was included into the analysis along with other baseline predictors (Model B) [21]. This would indicate that patients with advanced fibrosis or cirrhosis who carry the CC *IL28* genotype and present with low viremia are likely to respond favorably to PegIFN and RBV in the event they achieve an RVR. Finally, our data confirm patients with mild or moderate fibrosis and low viral load have the same probability of obtaining an SVR when treated for a short (24 weeks) or standard duration of therapy (48 weeks), as originally pointed out by Zeuzem *et al.* [22].

The major implication of recommending triple rather than dual therapy for the universal population of HCV 1 infected patients is that more patients would achieve viral load reduction at week 4, as shown by trials on combination therapy of a direct antiviral agent with PegIFN and ribavirin. However, because PegIFN and RBV can cause burdensome adverse effects and treatment is prolonged, HCV protease inhibitors will add significant morbidity. In this study, we estimated that 24.4% of 1045 patients with chronic HCV infection were capable to achieve RVR, a percentage in keeping with that reported in a recent systematic review of literature data on this topic [12]. These findings lend support to a risk-stratification of patients according to interferon responsiveness at treatment week 4 before the addition of protease inhibitors [1,2]. In order to optimize the risk/benefit ratio of combination therapies, we would recommend to initiate antiviral treatment in all naïve patients with chronic HCV infection, regardless of their presenting features, and to keep on with

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standard conventional therapy in those with RVR and other predictors of SVR.

In conclusion, the growing enthusiasm about embracing new therapies should not obscure the notion that an appreciable number of HCV-1 infected patients are able to eliminate the virus with conventional dual therapies. We estimated the magnitude of these patients to amount to 20%, a figure which is constituted by the great majority of patients experiencing RVR.

## Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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