Prediction of response to pegylated interferon plus ribavirin in HIV/hepatitis C virus (HCV)-coinfected patients using HCV genotype, IL28B variations, and HCV-RNA load

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Introduction

Infection with the hepatitis C virus (HCV) is frequently observed in the HIV-infected population due to shared routes of transmission [1]. The evolution of HCV-related hepatic disease is accelerated in the HIV-infected population, and hepatic complications currently represent a major cause of death among these patients in Western countries [2,3]. Successful anti-HCV therapy is associated with a regression in fibrosis evolution [4], as well as with a lower incidence of complications due to liver-related mortality [3,5]. However, the overall response to the current standard anti-HCV therapy with pegylated interferon (Peg-IFN) plus ribavirin (RBV) is particularly low in HIV-coinfected patients [6–8].

Recent studies have demonstrated that the single nucleotide polymorphism (SNP) rs12979860 near the interleukin 28B (IL28B) gene is a strong independent predictor of treatment response in HCV-monoinfected [9–12] and HIV/HCV-coinfected [13,14] patients. The consideration of IL28B genotype along with other well-defined pre-treatment determinants of response, such as HCV baseline viral load and HCV genotype, may improve the accuracy of sustained virologic response (SVR) prediction. Indeed, the combination of these three parameters, along with liver stiffness measured by transient elastography, have demonstrated a high diagnostic performance [15]. Thus, a predictive model (Prometheus) [15] has been developed accordingly. However, the Prometheus model does not distinguish between HCV genotype...
1 and 4 and requires fibrosis assessment by transient elastography, a procedure that is not available worldwide.

In a few years, directly acting agents (DAA) against HCV will be commercially available for the treatment of HIV/HCV-coinfected patients. The approval of protease inhibitors, the drug family that will be available earlier [16], is restricted to HCV genotype 1. However, other families with a broader spectrum of activity, such as nucleoside analogue polymerase or NNSA inhibitors, will likely be part of the anti-HCV armamentarium not much later. It is then conceivable that we will be able to use highly active anti-HCV therapies for most HIV/HCV-coinfected patients in a few years. Therefore, in the meantime, the accurate prediction of SVR to Peg-IFN plus RBV will be particularly important. Indeed, it is reasonable to defer therapy until more effective options are available in patients who are unlikely to respond to Peg-IFN plus RBV, at least if they do not show advanced fibrosis. Conversely, patients who have a high likelihood of achieving SVR to Peg-IFN plus RBV may be candidates for immediate treatment. Hence, reliable predictive tools that use a combination of accessible tests, which may accurately foresee SVR in a large proportion of patients, are needed.

The aim of this work was to elaborate an algorithm that could allow to define the probability of achieving SVR to HCV treatment with Peg-IFN plus RBV using viral genotype, IL28B genotype, and baseline plasma HCV-RNA without requiring transient elastography in HIV/HCV-coinfected subjects.

Patients and methods

Study population

The study population consisted of HIV/HCV-coinfected patients from four Spanish and one German cohorts prospectively followed in the Infectious Diseases Unit of three university hospitals in Southern Spain, a hospital in Madrid, Spain, and a university hospital in Bonn, Germany, from June 2000 to May 2010. All patients belonging to these cohorts were included in this study if they met the following criteria: (i) older than 18 years; (ii) completion of a full course of anti-HCV therapy for immediate treatment. Hence, reliable predictive tools that use a combination of accessible tests, which may accurately foresee SVR in a large proportion of patients, are needed.

The patients were randomly split by the statistical software in a 60/40 ratio to obtain two groups, one for the elaboration of the predictive algorithm and the other for its validation. Baseline characteristics of the two groups were compared using the Chi-square test for categorical variables and the Mann–Whitney U-test for continuous variables, respectively. All individuals were categorized in subgroups, firstly according to HCV genotype, secondly to the baseline HCV-RNA load and finally according to whether they were rs12979860 CC carriers or not. For each group, the rate of SVR was calculated. Patients with a likelihood of SVR of at least 60% were considered anticipated responders. Those who had a probability lower than 20% to achieve SVR were classified as unlikely responders. The remaining patients were considered uncertain responders. Considering SVR as the outcome variable, the predictive capacity of the algorithm was analyzed by means of receiver operator characteristic (ROC) curves generated from the model in the two groups. Anticipated responders developing SVR and unlikely responders who failed to achieve it were considered as patients correctly classified. Anticipated responders without SVR and unlikely responders showing SVR were considered failures of the algorithm. Likewise, the sensitivity, the specificity, the negative predictive value (NPV) and the positive predictive value (PPV) of this algorithm were calculated for those patients that were classified as unlikely or anticipated responders. The statistical analysis was carried out using the SPSS statistical software package release 195.0 (IBM Corporation, Somers, NY, USA) and STATA 9.0 (StataCorp LP, College Station, TX, USA).

Ethical aspects

The study was designed and performed according to the Helsinki declaration and was approved by the Ethics Committee of the five participating hospitals. All patients provided written informed consent to participate in this study.

Results

Characteristics of the study population

A total of 521 patients were included in this study. Among them, 236 (45.3%) patients carried rs12979860 genotype CC whereas 285 (54.7%) bore genotype CT or TT. Three hundred and twenty-one patients were randomly selected for the elaboration group, the remaining 200 individuals were included in the validation group. Further baseline characteristics are shown in Table 1.

Response to HCV therapy

In the overall population, 240 (46.1%; CI 95%; 41.7–50.5%) patients showed SVR. SVR was achieved in 151 (63.7%) patients showed genotype CC, 69 (30.1%) patients with genotype CT and 21 (37.5%) TT carriers, respectively (p <0.0001). The associations between SVR and HCV genotype, IL28B genotype, and baseline plasma HCV-RNA load are shown in Table 2.
Algorithm for SVR prediction

To develop the predictive algorithm, the patients of the elaboration group were categorized according to the three predictors of treatment response. The rates of SVR for each resulting category are shown in Fig. 1A. Thus, 132 (41.1%) patients were classified as anticipated responders. This group of patients included three subgroups: the first subgroup including all patients with viral genotype 2 or 3, regardless of the IL28B genotype and the baseline HCV-RNA load. The second one including patients with a viral genotype 4, who carried IL28B genotype CC, irrespective of the baseline HCV-RNA load, and the third subgroup including patients bearing HCV 1, with IL28B genotype CC, and baseline HCV-RNA load <600,000 IU/ml. Likewise, 87 (27.1%) individuals were identified as unlikely responders. These patients bore HCV genotypes 1 or 4, presented with a baseline HCV-RNA load of >600,000 IU/ml and were IL28B genotype CT or TT carriers. The remaining 102 (31.8%) patients were classified as uncertain responders. The predictive values of the algorithm in the elaboration population are shown in Table 3.

In the validation group, 90 (45%) patients showed a response rate of >60% and were classified as likely responders, while 63 (31.5%) were identified as unlikely responders (Fig. 1B). Forty-seven (23.5%) individuals were classified as uncertain responders. The predictive performance of the algorithm in this group was similar to that observed in the elaboration group (Fig. 2 and Table 3).

Frequency of the response categories

The frequency and the rate of SVR of the three categories of response were estimated in the overall population. Thus, 222 (42.6%) patients were classified as anticipated responders to therapy with Peg-IFN and RBV. The patients with viral genotype 2 or 3 showed a SVR rate of 74.1% (CI 95%: 66.5–80.7%), those bearing viral genotype 4 and IL28B genotype CC showed an SVR rate of 77.8% (CI 95%: 52.4–93.6%), while in patients harboring HCV 1, IL28B genotype CC, and baseline HCV-RNA load <600,000 IU/ml, the SVR rate was 67.4% (CI 95%: 52–80.5%). The overall SVR rate in the group of anticipated responders was 73% (CI 95%: 66.6–78.7%). Sixty (27%) patients in this group did not achieve an SVR and thus were misclassified. One hundred and fifty (28.8%) patients were identified as unlikely responders. Among them, 23 carriers (17.6%; CI 95%: 11.5–25.2%) of genotype 1, and three carriers (15.8%; CI 95%: 3.4–39.6%) of genotype 4 reached an SVR, while 124 (82.7%; CI 95%: 75.6–88.4%) patients did not reach an SVR. The misclassification rate was 17.3%, according to 26 patients showing SVR. A total of 149 (28.6%) patients were classified as uncertain responders. The overall rate of SVR in this sub-population was 34.9% (CI 95%: 27.3–43.1%).

Discussion

The combined use of IL28B genotype, HCV genotype, and baseline HCV-RNA load enables to identify patients with a high and a very low likelihood of response to anti-HCV treatment with Peg-IFN and RBV. Using these three variables, we developed an algorithm to predict the rate of SVR which may be applied in a broad range of institutions. This algorithm may help clinicians to make the decision of initiating treatment immediately with Peg-IFN plus RBV or deferring therapy, until more effective options are available.
Pre-therapy prediction of SVR is a major challenge in the current clinical practice. The data presented in this study may help to reduce the proportion of treatment failure. Thus, the algorithm allows the identification of patients with a probability of less than 20% to achieve SVR. In the unlikely responders (Fig. 3), it could be considered to defer HCV therapy until more effective options are available, provided that significant fibrosis is absent. Although HIV/HCV-coinfected patients progress considerably fast to higher fibrosis stages, approximately 50% do not show progression of one fibrosis stage in a three-year period [21]. Accordingly, liver fibrosis progression monitoring is an alternative choice, until new drugs can be prescribed to HIV/HCV-coinfected patients or progression of fibrosis is detected. On the other hand, patients that are classified as anticipated responders (Fig. 3) have an overall probability of 73% to be successfully treated with Peg-IFN/RBV. Therefore, in these patients it would be reasonable to start the bitherapy with Peg-IFN/RBV immediately. In the remaining patients (Fig. 3), individualized decisions should be made. Importantly, the predictive algorithm presented here may be useful for a high proportion of HIV/HCV-coinfected patients, as it allowed us to categorize 372 (71.4%) members of the population as anticipated or unlikely responders.

<table>
<thead>
<tr>
<th>Variable</th>
<th>SVR, No. (%)</th>
<th>p univariate</th>
<th>Adjusted OR (95% CI)</th>
<th>p multivariate</th>
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<tbody>
<tr>
<td><strong>HCV genotype</strong></td>
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<tr>
<td>1</td>
<td>100 (33)</td>
<td>&lt;0.0001</td>
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<tr>
<td>2-3</td>
<td>117 (76.6)</td>
<td>4.889 (3.12-7.65)</td>
<td>&lt;0.0001</td>
<td></td>
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<tr>
<td>4</td>
<td>23 (38.3)</td>
<td></td>
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<tr>
<td><strong>IL28B genotype</strong></td>
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<td></td>
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<tr>
<td>CC</td>
<td>151 (63.7)</td>
<td>&lt;0.0001</td>
<td>3.312 (2.23-4.9)</td>
<td>&lt;0.0001</td>
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<tr>
<td>TT or TC</td>
<td>89 (31.3)</td>
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<tr>
<td><strong>Baseline HCV-RNA load (IU/ml)</strong></td>
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<tr>
<td>&lt;600,000</td>
<td>111 (57.8)</td>
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*CI, confidence interval.

Pre-therapy prediction of SVR is a major challenge in the current clinical practice. The data presented in this study may help to reduce the proportion of treatment failure. Thus, the algorithm allows the identification of patients with a probability of less than 20% to achieve SVR. In the unlikely responders (Fig. 3), it could be considered to defer HCV therapy until more effective options are available, provided that significant fibrosis is absent. Although HIV/HCV-coinfected patients progress considerably fast to higher fibrosis stages, approximately 50% do not show progression of one fibrosis stage in a three-year period [21]. Accordingly, liver fibrosis progression monitoring is an alternative choice, until new drugs can be prescribed to HIV/HCV-coinfected patients or progression of fibrosis is detected. On the other hand, patients that are classified as anticipated responders (Fig. 3) have an overall probability of 73% to be successfully treated with Peg-IFN/RBV. Therefore, in these patients it would be reasonable to start the bitherapy with Peg-IFN/RBV immediately. In the remaining patients (Fig. 3), individualized decisions should be made. Importantly, the predictive algorithm presented here may be useful for a high proportion of HIV/HCV-coinfected patients, as it allowed us to categorize 372 (71.4%) members of the population as anticipated or unlikely responders.

In this predictive algorithm, the parameters taken into account are HCV genotype, IL28B genotype, and baseline

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**Table 2. Associations between SVR and HCV genotype, IL28B genotype and baseline HCV viral load in the univariate and multivariate analysis (n = 521).**

<table>
<thead>
<tr>
<th>Variable</th>
<th>SVR, No. (%)</th>
<th>p univariate</th>
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<th>p multivariate</th>
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<td>4</td>
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<td>&lt;0.0001</td>
<td>3.312 (2.23-4.9)</td>
<td>&lt;0.0001</td>
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<tr>
<td>TT or TC</td>
<td>89 (31.3)</td>
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<tr>
<td><strong>Baseline HCV-RNA load (IU/ml)</strong></td>
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<tr>
<td>&lt;600,000</td>
<td>111 (57.8)</td>
<td>&lt;0.0001</td>
<td>2.192 (1.46-3.29)</td>
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<tr>
<td>≥600,000</td>
<td>129 (39.2)</td>
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*CI, confidence interval.

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**Table 3. Predictive performance of the algorithm in patients classified as anticipated or unlikely responders.**

<table>
<thead>
<tr>
<th></th>
<th>Overall population (n = 521)</th>
<th>Elaboration group (n = 321)</th>
<th>Validation group (n = 200)</th>
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<tr>
<td>Sensitivity (%)</td>
<td>86.2</td>
<td>87.3</td>
<td>84.6</td>
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<tr>
<td>Specificity (%)</td>
<td>67.4</td>
<td>67</td>
<td>68</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>73</td>
<td>72.7</td>
<td>73.3</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>82.7</td>
<td>83.9</td>
<td>81</td>
</tr>
<tr>
<td>Misclassified patients, n (%)</td>
<td>86 (23.1)</td>
<td>50 (22.8)</td>
<td>36 (23.5)</td>
</tr>
</tbody>
</table>

Fig. 1. Rates of SVR according to viral genotype (GT), IL28B genotype, and baseline HCV-RNA load. (A) Elaboration group (n = 321); (B): validation group (n = 200).
HCV-RNA load (Fig. 3). The predictive performance of this algorithm is somewhat lower than that yielded by the Prometheus model, which, in addition to these three parameters, also evaluates liver stiffness, as determined by transient elastometry [15]. However, the Prometheus index does not differentiate between genotype 1 and 4. This is a limitation, because genotype 4 may account for up to 15% in HIV/HCV-coinfection in some settings [22] and the rate of SVR in patients with HCV genotype 4 is slightly higher. Furthermore, transient elastometry is expensive and not approval worldwide.

A further procedure to predict treatment success is monitoring viral kinetics during therapy with Peg-IFN/RBV. In this context, viral response at week 4 of treatment has high PPV and NPV [23]. Thus, it has been demonstrated that 95% of the patients who present with rapid virological response (RVR), defined as undetectable plasma HCV-RNA viral load at week 4 of therapy, achieve an SVR [23]. Conversely, a decline in plasma HCV-RNA load of <0.6 log units has an NPV of 96% [23]. Furthermore, a threefold higher treatment success rate was observed in those patients who reached undetectable HCV-RNA at week 12 [24], while a decline of plasma HCV-RNA lower than 2 log units at this time point has an NPV close to 100% [6]. Nevertheless, very few genotype 1 patients show RVR [23] and less than one third of genotype 1 or 4 carriers present with a decline in plasma viral load of <0.6 log_{10} IU/ml at week 4 of therapy [23]. Therefore, plasma HCV-RNA decline at week 4 allows us to classify only a minority of patients. The assessment of viral kinetics requires exposure to treatment up to 12 weeks. This implies to administer therapy during the period when side effects are more common and severe. Therefore, whenever possible, it is preferable to apply pre-therapy predictive strategies as that presented in this work to spare treatment in those with lower chance to respond.

This study has some limitations. First, this algorithm may be obsolete relatively soon, since triple therapy with DAA/Peg-IFN/RBV will likely be standard-of-care in the near future. However, NS3 protease inhibitors are specific for HCV genotype 1 and bitherapy with Peg-IFN/RBV will still be the treatment strategy in genotype non-1 carriers for several years. Furthermore, drug-drug interactions with antiretroviral treatment may preclude the use of protease inhibitors in a significant proportion of HIV/HCV-coinfected patients [25] and the rate of SVR will probably be lower in the HIV-coinfected population. Thus, pre-therapy prediction of SVR will likely be more important in HIV-coinfected than in monoinfected patients. Moreover, the thresholds selected here to define the response categories are arbitrary. However, response rates of 20% and 60% are reasonable cut-off points to consider patients as good or poor responders. In addition, the proportion of genotype 4 carriers was considerably small, which reflects the HCV genotype distribution in our environment [26–27] and studies with larger sample sizes of this subset are necessary. In fact, an ongoing multicentric study in our area aims to recruit more patients bearing HCV genotype 4 (unpublished data). Furthermore, the HCV genotype and the baseline viral load are well studied predictors of SVR and might have caused a selection bias in the population of this study. However, the genotype

![Fig. 2. Diagnostic performance of the predictive index of sustained virological response in accordance with the HCV genotype, the IL28B SNP rs12979860, and the baseline viral load. Continuous line: overall population, area under the receiver operating characteristic curve [AUROC (95% CI)]: 0.77 (0.733–0.814), n = 521; dashed line: elaboration group, AUROC (95% CI): 0.77 (0.723–0.826), n = 321; dotted line: validation group, AUROC (95% CI): 0.77 (0.708–0.841), n = 200.](image)

![Fig. 3. Stepwise algorithm for the classification of patients as anticipated, unlikely and uncertain responders to bitherapy with peg-IFN/RBV in accordance with the HCV genotype, the baseline HCV load, and the IL28B genotype.](image)
distribution reported herein is similar to that reported in epide-
miological studies conducted in this environment [26–27].
Therefore, we believe that our results are extrapolable to the glo-
bal HIV/HCV-coinfected population since no significant deviation
can be expected. In any case, the strategy of categorizing subjects
according to HCV and IL28B genotypes as well as HCV-RNA load
allows to define an accurate probability of response in specific
subpopulations (Figs. 1 and 2), and enables to use further deci-
sion criteria in individual cases, if required. To our knowledge,
the sample size of this study is the biggest for a predictive
strategy in HIV/HCV-coinfection. Furthermore, this algorithm
identifies a proportion of over 70% of patients in whom a catego-
rization as unlikely or anticipated responders can be made, with
a fairly low rate of misclassification, without needing fibrosis
assessment. Finally, the model was validated by a separate group
of patients. These represent the strengths of this study.

In conclusion, this work presents a simple and reliable pre-
therapy tool to identify unlikely and anticipated responders to
treatment with Peg-IFN plus RBV in HIV/HCV-coinfected patients,
including three blood parameters. Two of these parameters were
routinely used many years ago and the other has been recently
incorporated into clinical practice. This tool may be used to select
HIV/HCV-coinfected candidates for immediate and, more impor-
tantly, deferred therapy against HCV and it is able to identify as
anticipated or unlikely responders in up to approximately three
quarters of patients.

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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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