Response to interferon-based therapies in HIV-infected patients with chronic hepatitis C due to genotype 4

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Background: The hepatitis C virus (HCV) genotype is the main predictor of response to interferon (IFN)-based therapies. HCV genotype 4 is spreading among European intravenous drug users, who are frequently coinfected with HIV. Information about treatment response in this subset of patients is scarce and conflicting results have been reported.

Methods: All HIV-infected patients treated for chronic hepatitis C at our institution with a minimum follow-up of 6 months after discontinuing therapy were retrospectively analysed. They had received one of three HCV treatment modalities: IFN monotherapy, IFN plus ribavirin (RBV) or pegylated interferon (PEG-IFN) plus RBV. Treatment responses were stratified according to HCV genotype.

Results: A total of 390 patients were analysed. Sustained virological response (SVR) to HCV therapy had been reached by 90 (23.1%): 22/119 (18.5%) with IFN monotherapy; 17/106 (16%) with IFN plus RBV; and 51/165 (30.9%) with PEG-IFN plus RBV. SVR was significantly higher among those with HCV genotypes 2 or 3 (40.4%; 61/151) than in patients with either HCV genotype 1 (11.2%; 22/197) or HCV genotype 4 (16.7%; 7/42) (P<0.0001). In contrast, there were no significant differences in the response rate comparing HCV genotypes 1 and 4 (P=0.53).

Conclusions: Response to IFN-based therapies in HIV-positive patients with hepatitis C due to HCV genotype 4 is poor, similar to that obtained for HCV genotype 1 and much lower than for HCV genotypes 2 and 3. Therefore, HIV-infected patients with hepatitis C due to genotype 4 should be considered as a particular subset of difficult-to-treat patients. New treatment strategies and drugs for these patients are eagerly awaited.

Introduction

Chronic hepatitis C is currently one of the leading causes of hospital admission and death among HIV-positive patients, particularly in regions where intravenous drug users represent a large proportion of the HIV-infected population [1–4]. Treatment of hepatitis C in HIV-infected individuals has only recently begun to be recognized as a priority [5]. However, the limitations of current HCV therapy in coinfected individuals have not been fully appreciated until recently. Among them, two main drawbacks merit particular attention. The first is the relatively low response uniformly seen across trials conducted so far in HCV/HIV-coinfected patients, even using pegylated interferon (PEG-IFN) plus ribavirin (RBV) [5–8]. The second is the report of unexpected adverse events, mainly due to the interaction of RBV with some anti-HIV compounds (for example, didanosine and/or stavudine), including hyperlactataemia, pancreatitis and severe weight loss [9,10].

The achievement of sustained virological response (SVR), defined as clearance of serum HCV-RNA 6 months after discontinuing HCV therapy, has been interpreted as a cure for HCV infection [11,12]. However, this outcome is reached by only 40% of HCV-monoinfected patients with HCV genotype 1 and by twice as many subjects with HCV genotypes 2 or 3 using the current standard treatment [13,14]. For patients infected with HCV genotype 4, the information available so far is scarce and, more importantly, conflicting results have been reported. While some authors have claimed that patients infected with HCV genotype 4 may respond quite well to IFN-based therapies, others have not confirmed these findings [14–19]. Moreover, data on treatment response for genotype 4 in HCV/HIV-coinfected patients are only anecdotal. This information, however, is relevant since between 10% and 20% of HIV-positive patients in Western Europe are infected with HCV genotype 4 [20–26].
Patients and methods

All subjects enrolled in four different clinical trials evaluating HCV therapy in HIV-positive patients conducted in Spain and previously reported [27–30], along with 97 HCV/HIV-coinfected individuals treated more recently at our institution with PEG-IFN plus RBV, following doses and schedules used in a prior trial [30], were analysed.

Briefly, the first study included 90 HIV-infected individuals enrolled in 1992 in a trial of treatment with IFN monotherapy at doses of 3 MU three times per week [27]. A second study evaluated the efficacy and safety of escalating doses of IFN monotherapy in 29 coinfected patients [28]. A third study conducted in 2000 assessed the performance of IFN three times a week plus RBV 400 mg twice daily in 106 coinfecte d individuals [29]. Finally, the most recent trial examined the efficacy of PEG-IFN alpha 2b 1.5 mg per week plus RBV 400 mg twice daily in 68 patients [30]. In all these trials, coinfect ed patients with positive hepatitis B surface antigen, CD4 counts below 200 cells/µl, active drug addiction or alcohol abuse were excluded.

HCV genotyping had been performed in all those trials using a commercial hybridization assay (Inno-LiPA; Innogenetics, Ghent, Belgium). Plasma HCV-RNA had been measured using a RT-PCR commercial test (Amplicor Monitor HCV; Roche, Basel, Switzerland).

Statistical analysis

Qualitative variables are expressed as absolute values and percentages. Continuous variables are expressed as mean values. Means were compared using the Mann-Whitney rank sum test. Categorical variables were compared using the chi-square or Fisher’s exact tests. For the purpose of this study, relapers and non-responders were considered together, since all had detectable serum HCV-RNA 6 months after discontinuing HCV therapy. All P values were 2-tailed and differences were considered as significant when P was below 0.05. All data analyses were conducted using the SPSS for Windows, v10.0 (SPSS, Inc., Chicago, IL, USA).

Results

A total of 390 HCV/HIV coinfected patients were analysed. Overall, 71% were male, 81% had been intravenous drug users, mean age was 35 years (±7), mean weight was 66 kg (±7), 97% were Caucasians, the mean CD4 count was 498 cells/µl (±211), 62% were on antiretroviral therapy at the time of initiating their IFN-based therapy and 61% had plasma HCV-RNA above 800 000 IU/ml. Table 1 summarizes the main features of the study population according to the HCV genotype distribution.

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of the study population</th>
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<tbody>
<tr>
<td>HCV genotype</td>
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<tr>
<td>--------------</td>
</tr>
<tr>
<td>Number of patients (n=390)</td>
</tr>
<tr>
<td>Treatment modality</td>
</tr>
<tr>
<td>IFN monotherapy (n=119)</td>
</tr>
<tr>
<td>IFN plus RBV (n=106)</td>
</tr>
<tr>
<td>PEG-IFN plus RBV (n=165)</td>
</tr>
<tr>
<td>Male gender, %</td>
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<tr>
<td>Mean age, years</td>
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<tr>
<td>Past intravenous drug use, %</td>
</tr>
<tr>
<td>Caucasian ethnicity, %</td>
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<tr>
<td>Mean weight, kg</td>
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<tr>
<td>Mean CD4 count, cells/µl</td>
</tr>
<tr>
<td>On antiretroviral therapy, %</td>
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<tr>
<td>Serum HCV-RNA &gt;8 x 10^5 IU/ml, %</td>
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</table>

IFN, interferon; RBV, ribavirin; PEG-IFN, pegylated interferon; HCV, hepatitis C virus.

HCV infection due to genotype 1 was the most common (50.5%), followed by genotypes 2 and 3 (38.7%) and genotype 4 (10.8%). Overall, there were no statistically significant differences in baseline characteristics comparing patients with distinct HCV genotypes.

SVR to HCV therapy was reached by 90 (23.1%) patients: 22/119 (18.5%) with IFN monotherapy; 17/106 (16%) with IFN plus RBV; and 51/165 (30.9%) with PEG-IFN plus RBV. When considering HCV genotypes separately, the SVR was obtained by 22/197 (11.2%) of patients with genotype 1, 61/151 (40.4%) with genotypes 2 or 3 and 7/42 (16.7%) with genotype 4 (see Figure 1).
Treatment of hepatitis C due to genotype 4 in HIV patients

The difference in SVR between patients with HCV genotypes 2 or 3 and those with HCV genotypes 1 or 4 was strongly significant \((P<0.0001)\). In contrast, there were no significant differences comparing the response in patients with HCV genotype 1 and in those with genotype 4 \((P=0.53)\). This difference in treatment response comparing patients with HCV genotypes 2 and 3 to those with HCV genotypes 1 and 4 was seen across distinct HCV treatment modalities (Figure 1).

Discussion

Chronic hepatitis C affects more than three-quarters of HIV-positive individuals infected parenterally, mainly intravenous drug users [5]. Although infection with HCV genotypes 2 and 3 has been classically linked to this population, recent surveillance studies in Europe have highlighted the spread of the HCV genotype 4 [22–26]. While responses above 75% have been reported for patients infected with HCV genotypes 2 and 3 treated with PEG-IFN plus RBV and below 50% for subjects with HCV genotype 1, the results for subjects carrying HCV genotype 4 are conflicting. While some authors have reported rates of SVR between 77% and 79% [14,15], others have not confirmed it, highlighting the fact that HCV genotype 4 patients, like those with genotype 1, should be considered as a difficult-to-treat population [16–19]. Differences in RBV doses and use of distinct pegylated interferon molecules in those studies could in part explain their discordant results.

This uncertainty about the treatment outcome is even more pronounced for genotype 4 individuals coinfected with HIV. The largest trial reported so far in HCV/HIV-coinfected patients, the APRICOT study [8], has not specifically analysed the results obtained in 7% of the 868 patients recruited in the trial who carried HCV genotype 4. The information on this genotype is relevant since good responders might be considered a difficult-to-treat population [16–19].

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Our results support that the SVR is quite similar in subjects infected with HCV genotypes 1 and 4, and is poor overall irrespective of the IFN-based treatment modality. As expected, patients treated with PEG-IFN plus RBV were those who attained more favourable outcomes, but this was true for all HCV genotypes. However, even using the currently recommended combination treatment of PEG-IFN plus RBV, no more than one-quarter of HIV coinfected patients with HCV genotype 4 reached SVR, which was clearly below the 61% achieved treating HCV genotype 2 and 3 patients.

Several studies have shown that SVR is strongly associated with the speed of the initial HCV-RNA decay under treatment [31]. In this respect, our findings are in agreement with a recent report examining early kinetics in HCV genotype 4 under IFN, concluding that it was comparable to that seen in patients with genotype 1 but significantly slower than for genotype 2 [19].

Our study, however, has several limitations. The most important is its retrospective design, with pooled data from three trials dating back to 1992. Even though 390 patients were analysed overall, only 42 of them carried HCV genotype 4. Taking into account the overall low response rate associated with non-pegylated IFN, the power of the study is relatively low in making definitive conclusions on differences between virological response rates according to the different genotypes. Therefore, further studies restricting the analysis to pegylated IFN trials should be conducted to reach more precise conclusions.

In summary, our results highlight that HCV genotype 4 patients should be considered as poor responders to IFN-based therapies and therefore treatment rules applied to HCV genotype 1 patients should be similarly followed in them, including the administration of at least 1 year of therapy in early virological responders. Given the faster progression to end-stage liver disease in HCV/HIV-coinfected individuals [32], new treatment strategies and new HCV drugs are urgently needed to improve the sustained virological response rates in this population, in which HCV genotype 4 is particularly prevalent.

Acknowledgements

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