Short communication

Predicted effect of direct acting antivirals in the current HIV–HCV-coinfected population in Spain

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Background: Direct acting antivirals (DAAs) against HCV are eagerly awaited for HIV–HCV-coinfected individuals. However, the activity of first generation drugs is limited to HCV genotype 1 and is lower in cirrhotics, subtype 1a infections, prior interferon (IFN)-α exposure or unfavourable IL28B alleles. Herein, we report the current profile of HIV–HCV-coinfected patients at our institution in an attempt to predict the effect of DAAs.

Methods: All HIV–HCV-coinfected patients seen at our HIV outpatient clinic in 2011 were identified. Information on serum HCV RNA, HCV genotype/subtype, plasma HIV RNA, prior IFN-α experience, liver fibrosis staging and IL28B alleles was recorded.

Results: A total of 424 HIV–HCV-coinfected patients were identified, of whom 174 (41%) were IFN-α-experienced. Mean serum HCV RNA was 6 log IU/ml. HCV genotype/subtype distribution was 166 (39.1%) G1a, 93 (22%) G1b, 85 (20%) G4, 49 (11.5%) G3 and 1 (<1%) G2, and 30 (7%) were unclassified. Of note, 56% of G1a were prior IFN-α-experienced patients. Overall, 37% had advanced liver fibrosis (Metavir score estimates F3–F4). Finally, 70% harboured unfavourable IL28B alleles.

Conclusions: The current profile of HIV–HCV-coinfected patients in Spain is dominated by particularly difficult-to-treat individuals, such as those infected with G1a or G4 (59%), advanced liver fibrosis (37%) and unfavourable IL28B alleles (70%). A wide use of prior anti-HCV therapy in our region most likely has resulted in hepatitis C cure of more IFN-α susceptible individuals, with accumulation of a more refractory treatment population. Thus, the use of DAAs in HIV–HCV-coinfected patients will require particular expertise and their benefit might be lower than expected.

Introduction

Chronic HCV infection affects a quarter of HIV-infected individuals in Western Europe [1]. Liver disease evolves more rapidly in this population as compared to HCV-monoinfected individuals [2]. The immune recovery associated with the use of potent antiretroviral therapy ameliorates the negative effect of HIV on HCV-related liver fibrosis progression [3], although there is no complete normalization [4], as development of cirrhosis and hepatic complications are still among the leading causes of death in HIV–HCV-coinfected patients [5,6].

By contrast with HIV, which cannot be eradicated, successful treatment of HCV infection leads to sustained elimination of the virus [7]. The combination of pegylated interferon (IFN)-α plus ribavirin has been the only available therapeutic option for chronic hepatitis C during the last decade [8,9]. This medication, however, has limited efficacy and is frequently associated with serious adverse events [8,9]. For this reason, the advent of new direct acting antivirals (DAAs) against HCV is eagerly awaited for the treatment of chronic hepatitis C in HIV-coinfected individuals. These drugs are administered orally, generally for short periods and result in cure in >75% of treated individuals [10–13]. However, the antiviral activity of most DAAs is restricted to infections caused HCV genotype 1 variants [14] and tends to be lower in the subset of patients with prior IFN-α experience, advanced liver fibrosis and/or unfavourable IL28B gene polymorphisms [15–20]. The aim of this study was to characterize the main features of a large group of HIV-infected individuals with chronic hepatitis C seen at a reference HIV outpatient clinic in Madrid, Spain, in an attempt to predict what will be the effect of introducing DAAs in this population.

Methods

Study population
All HIV–HCV-coinfected patients with positive serum HCV RNA seen at our institution during the first
The extent of liver fibrosis had been measured during the prior 12 months in all patients using transient elastography by FibroScan® (Echosens®, Paris, France). Details about this non-invasive method, the examination procedure, and correlation of liver fibrosis estimates with liver biopsy have been reported elsewhere [22,23]. The median value of all tests per patient is expressed in kPa units. According to previous studies conducted in HIV–HCV-coinfected patients [24–26], cutoff values fitting the best with Metavir scores were as follows: <7.2 kPa for null or minimal liver fibrosis (Metavir F0–F1), 7.2–9.5 kPa for moderate liver fibrosis (Metavir F2), 9.6–14.5 kPa for advanced liver fibrosis (Metavir F3) and >14.5 kPa for cirrhosis (Metavir F4).

### IL28B rs12979860 genotyping

DNA specimens collected from peripheral blood mononuclear cells for each individual were genotyped using the 5′ nuclease assay with allele specific TaqMan probes (ABI TaqMan allelic discrimination kit; Applied Biosystems, Carlsbad, CA, USA) and the ABI-7900HT Sequence Detection System (Applied Biosystems) [27]. Genotyping was blinded and calls were manually inspected and verified prior to release. The results were reported as three categories: CC, CT or TT. As prior studies have uniformly shown that IL28B allelic threats behave as an autosomal recessive inheritance [28–33], CT and TT were considered together.

### Statistical analyses

The main characteristics of the study population and the different parameters evaluated are expressed as mean ± SD or proportions. All statistical analyses were performed using the SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA). All P-values were two-tailed, and were considered as significant only when <0.05.

### Results

A total of 424 HIV–HCV-coinfected patients with positive serum HCV RNA were identified. Their main characteristics are recorded in Table 1. The majority were male (72.2%) and white (96.6%). Their mean age was 45 years. Most (77.4%) had been intravenous drug users in the past. Overall, 87% were on antiretroviral therapy. Their mean CD4+ T-cell count was 369 ± 541 cells/µl and 73.1% of subjects had plasma HIV RNA<50 copies/ml.

Overall 174 (41%) coinfected patients had previously been exposed to IFN-α. Their current mean ± SD serum HCV RNA was 6 ± 0.9 log IU/ml. The HCV genotype/subtype distribution was as follows: 166 (39.1%) G1a, 93 (22%) G1b, 85 (20%) G4, 49 (11.5%) G3 and 1 (<1%) G2, and 30 (7%) were unclassified. Of note, 56% of G1a were prior IFN-α-experienced. Overall, 223 (53%) patients had significant (Metavir score estimates ≥F2) and 158 (37%) had advanced (Metavir score estimates F3–F4) liver fibrosis. Among patients with advanced liver fibrosis, the most prevalent genotype/subtypes were G1a and G4.

### Table 1. Main characteristics of the study population including 424 HIV–HCV-coinfected patients with positive serum HCV RNA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>306 (72.2)</td>
</tr>
<tr>
<td>Mean age, years (±sd)</td>
<td>45 (6)</td>
</tr>
<tr>
<td>Prior intravenous drug use, n (%)</td>
<td>328 (77.4)</td>
</tr>
<tr>
<td>Caucasian ethnicity, n (%)</td>
<td>342 (96.6)</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
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<tr>
<td>Antiretroviral therapy, n (%)</td>
<td>369 (87)</td>
</tr>
<tr>
<td>Mean CD4+ T-cell count, cells/µl (±sd)</td>
<td>541 (318)</td>
</tr>
<tr>
<td>Plasma HIV RNA&lt;50 copies/ml, n (%)</td>
<td>310 (73.1)</td>
</tr>
<tr>
<td>HCV status</td>
<td></td>
</tr>
<tr>
<td>Prior interferon-α experience, n (%)</td>
<td>174 (41)</td>
</tr>
<tr>
<td>Mean serum HCV RNA, log IU/ml (±sd)</td>
<td>6 (0.9)</td>
</tr>
<tr>
<td>HCV genotype/subtype</td>
<td></td>
</tr>
<tr>
<td>1a, n (%)</td>
<td>166 (39.1)</td>
</tr>
<tr>
<td>1b, n (%)</td>
<td>93 (22)</td>
</tr>
<tr>
<td>2, n (%)</td>
<td>1 (0.002)</td>
</tr>
<tr>
<td>3, n (%)</td>
<td>49 (11.5)</td>
</tr>
<tr>
<td>4, n (%)</td>
<td>85 (20)</td>
</tr>
<tr>
<td>Unclassified, n (%)</td>
<td>30 (7)</td>
</tr>
<tr>
<td>Liver fibrosis staging</td>
<td></td>
</tr>
<tr>
<td>Significant (Metavir ≥F2), n (%)</td>
<td>223 (52.6)</td>
</tr>
<tr>
<td>Advanced (Metavir F3–F4), n (%)</td>
<td>158 (37.3)</td>
</tr>
<tr>
<td>IL28B rs12979860 CT/TT alleles, n (%)</td>
<td>194 (40)</td>
</tr>
</tbody>
</table>

aData are available for 354 patients. bData are available for 279 patients.
(58.2%). Finally, 70% of patients harboured IL28B CT/TT alleles.

The cumulative proportion of patients with predictors of reduced DAA activity, such as G1a infection, prior IFN-α exposure, prior IL28B CT/TT alleles and/or advanced liver fibrosis is recorded in Figure 1. It is noteworthy that nearly two-thirds (32.5%) of the whole study population had 3 or 4 of these predictors of poor treatment response. Conversely, only 38.2% had ≤1 predictor of poor response, and potentially could benefit more from DAA therapy. However, half of this last group of patients were infected with G3 and G4, genotypes for which first-generation DAAAs are not active [14].

Discussion

The approval of oral DAAs as therapy for chronic hepatitis C is eagerly anticipated for HIV–HCV-coinfected individuals. However, the activity of first generation HCV protease inhibitors telaprevir and boceprevir is limited to HCV genotype 1 and is diminished in patients with cirrhosis, infection with subtype 1a, prior IFN-α exposure, or IL28B rs12979860 CT/TT gene polymorphisms [15–20]. In our study, we characterized the profile of current HIV–HCV-coinfected patients in Madrid, Spain, and found that it is dominated by particularly difficult-to-treat individuals, such as those infected with G1a or G4 (59%), significant liver fibrosis staging (53%) and IL28B CT/TT alleles (70%). A wide use of anti-HCV therapy in our region most likely has resulted in hepatitis C cure of more IFN-α susceptible individuals in the past [34], with accumulation of a more refractory treatment population.

It is noteworthy that HCV subtype 1a was by far the most frequent viral variant in our population, accounting for >39% of infections. Several studies testing the activity of HCV protease inhibitors have shown that earlier selection of viral mutants at the NS3 protease codon 155 largely drives more frequent failure in HCV subtype 1a than 1b [35,36]. Failure also seems to occur more commonly in G1a than G1b using HCV non-nucleoside polymerase inhibitors [36,37] and NS5A inhibitors [38], most likely as result of a higher prevalence of natural polymorphisms that may compromise the activity of some of these medications in G1a than in G1b viruses [39,40]. Moreover, in our population, within IFN-α-experienced patients having advanced liver fibrosis, 71% of HCV G1a patients harboured IL28B CT/TT alleles. Thus, we predict that virological failures using DAAs in our coinfected population might be more common, largely as result of this disproportionate prevalence of HCV subtype 1a with advanced liver fibrosis, and unfavourable IL28B alleles. In this regard, it would be worthy to collect information about HCV genotype/subtype distribution in other HIV–HCV-coinfected series.

It must be acknowledged that besides HCV-related characteristics, which were the focus of our study, the predicted effect of DAAs on the HIV–HCV-coinfected population may be influenced by other factors. The potential for drug interactions using DAAs in patients receiving antiretroviral therapy is currently one of the major concerns [41,42]. Although the information available is still too preliminary, significant and often unexpected pharmacokinetic interactions have already been reported between HCV protease inhibitors telaprevir and boceprevir and some HIV protease inhibitors boosted with ritonavir as well with efavirenz [43–45]. Although dose-adjustments may overcome some of these interactions, in some situations this is impossible. By contrast, pharmacodynamic interactions, such as those recognized and/or expected combining some nucleoside/nucleotide analogues active against either HIV or HCV will preclude their concomitant use [42]. This is the case for mericitabine and lamivudine or emtricitabine.

There are other considerations that may further add complexity to the use of DAAs for treating chronic hepatitis C in the HIV population, and that may ultimately reduce the global benefit of these drugs in this subset of patients. This is the case for overlapping toxicities of some antiretroviral agents and DAAs, with increased risk of anaemia or rash [41]. By contrast, excellent drug compliance might become problematic for some individuals when polymedication requires a high pill burden and several daily doses.

In summary, the current profile of HIV–HCV-coinfected patients in Madrid is dominated by particularly difficult-to-treat individuals, such as those infected with G1a or G4, advanced liver fibrosis staging
and unfavourable IL28B alleles. A wide use of anti-HCV therapy in the past in our region most likely has resulted in hepatitis C cure of more IFN-α susceptible individuals, with accumulation of a more refractory treatment population. Thus, the use of DAs in HIV–HCV-coinfected patients will require particular expertise and we predict that the global benefit will be lower than expected in this population.

Acknowledgements

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EP and VS designed the study. EV, PB, PL and JVF-M recorded the clinical and demographic information. CdM did the laboratory analyses. EP, EV and LM-C performed the statistical analyses. EP and VS wrote the manuscript draft. All authors revised and contributed to the final version.

Disclosure statement

The authors declare no competing interests.

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