Nevirapine-based Antiretroviral Therapy is Associated with Lower Plasma Hepatitis C Virus Viral Load among HIV/Hepatitis C Virus-Coinfected Patients

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Abstract

Objective: The aim of this study was to assess the relationship between the use of protease inhibitor (PI)-, nevirapine (NVP)- and efavirenz (EFV)-based antiretroviral therapy (ART) and plasma hepatitis C virus (HCV) viral load in a population of HIV/HCV-coinfected patients.

Patients and Methods: We examined the relationship between the use of NVP-, PI- and EFV-based ART and the plasma HCV viral load in HIV-infected patients without previous therapy against HCV.

Results: The median HCV-RNA level (log10 IU/mL) was significantly lower in patients receiving NVP (5.7; Q1-Q3, 5.2-5.8) than in subjects treated with EFV (6.0; Q1-Q3, 5.5-6.5) and in individuals receiving PIs (6.1; Q1-Q3, 5.5-6.7) (p<0.016).

Conclusions: HCV/HIV-coinfected individuals under NVP-based ART show lower plasma HCV-RNA levels than those receiving other regimens.

Keywords: HIV; HCV; Nevirapine; Antiretroviral therapy; HCV viral load

Introduction

A low plasma hepatitis C virus (HCV) load at starting pegylated interferon (peg-IFN) plus ribavirin (RBV) has been associated with a higher rate of sustained virological response (SVR) among HIV/HCV-coinfected individuals [1-4]. Due to this, the identification of factors related to lower HCV-RNA levels may help us to improve the outcome of therapy against HCV infection in this population. In this regard, it has been reported that patients who receive protease inhibitors (PIs)-based antiretroviral therapy (ART) show a higher HCV viremia than those treated with other regimens, mainly those including non-nucleoside reverse transcriptase inhibitors (NNRTI) [5]. Accordingly, the rate of response to hepatitis C therapy was lower among patients taking PIs in the Ribavic trial [2]. However, the latter finding has not been confirmed in other studies [6,7]. In addition, the specific influence of each NNRTI, specifically nevirapine (NVP) and efavirenz (EFV), on HCV-RNA levels remains unknown. Due to this, further investigations dealing with this topic are required.

The aim of this study was to assess the relationship between the use of PI-, NVP- and EFV-based ART and plasma HCV-RNA in a population of HIV/HCV-coinfected patients.

Patients and Methods

All HIV/HCV-coinfected patients who received peg-IFN plus RBV along with a PI- or NNRTI-based ART at thirteen hospitals in Spain from January 2004 to December 2008, were included in this retrospective cross-sectional study. Measurements of plasma HCV-RNA load were performed at baseline, before starting peg-IFN plus RBV, using a commercial PCR assay (Cobas Taqman; Roche Diagnostic Systems Inc., Pleasanton, CA, USA; detection limit of 50 IU/mL). The Kruskal-Wallis test and the Chi-square test for RxC tables were used to compare continuous variables and categorical variables, respectively. Post-hoc comparisons between groups were carried out using the Mann-Whitney U test and the Chi-square test for tables 2x2. Associations with a p value <0.05 were considered significant for comparisons among groups. The correction of Bonferroni was applied for the comparisons between groups in the post-hoc analysis. For these comparisons a p value <0.016 was considered significant. The Pearson r coefficient was used to examine the correlation between the levels of HCV viremia and the length of exposure to NVP- or PIs and the time with undetectable HIV viral load.

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Results

Three hundred and sixty patients were included in this study. Twenty-four (7%) individuals were treated with NVP, 176 (49%) subjects with EFV and 160 (44%) patients received Pi-based ART [66 (41%) lopinavir/ritonavir, 36 (22%) saquinavir/ritonavir, 26 (16%) atazanavir/ritonavir, 16 (10%) nelfinavir, 8 (5%) fosamprenavir/ritonavir, 3 (2%) amprenavir, 3 (2%) indinavir, 1 (1%) tipranavir/ritonavir and 1 (1%) subject darunavir/ritonavir]. The most relevant characteristics are shown in Table 1. The median time of exposure to NVP, EFV or Pi-containing regimens was 24.9 (Q1-Q3, 9.2-53.0) months, 32.2 (Q1-Q3, 12.8-50.6) months, and 17.3 (Q1-Q3, 4.0-35.6) months, respectively (p = 0.001). The median time with undetectable HIV load was 54.8 (Q1-Q3, 27.0-80.0) months in the NVP group, 40.7 (Q1-Q3, 20.1-57.1) months in the EFV group and 26.3 (Q1-Q3, 14.5-53.0) months in the PI group (p = 0.033). There were no statistically significant differences in other variables among the three treatment groups (Table 1).

The median HCV-RNA level was 6.1 (Q1-Q3, 5.8-6.7) log_{10} IU/mL in the 238 patients with HCV genotype 1 or 4 and 5.7 (Q1-Q3, 5.3-6.2) log_{10} IU/mL in the 122 subjects with genotype 2 or 3 (p = 0.001). The median HCV-RNA level in the NVP group was 5.7 (Q1-Q3, 5.2-5.8) log_{10} IU/mL, 6.0 (Q1-Q3, 5.5-6.5) log_{10} IU/mL in the EFV group, and 6.1 (Q1-Q3, 5.5-6.7) log_{10} IU/mL in the PI group (p = 0.016). In the one-to-one analysis, the difference between EFV and NVP group was slightly above the level of significance (p = 0.023), whereas between NVP and PI was significant (p = 0.007). Seventeen (71%) patients on NVP had a plasma HCV-RNA load below 600000 IU/mL vs 67 (38%) subjects on EFV and vs 62 (39%) individuals on PI (p for the table 3x2 = 0.007). The difference between patients taking NVP and those who received EFV was statistically significant (p = 0.002) as was that between subjects on NVP and those treated with PI (p = 0.003). HCV-RNA levels did not correlate with the time from starting NVP, EFV or PI (r = 0.117), nor with the duration of undetectable HIV viral load (r = 0.103).

Discussion

In this study, HCV/HIV-coinfected individuals who received NVP-based ART showed lower plasma HCV-RNA levels than those who were treated with EFV- or PI-containing regimens. Bani-Sadr et al. [5] had reported previously that PI-based ART is related to an increased in HCV load [5]. Nevertheless, data regarding the specific impact of NVP and EFV on plasma HCV-RNA were not assessed in the former study [5]. Thus, this is the first study, to our knowledge, showing an association between NVP treatment and plasma HCV viremia in the HIV/HCV-coinfected population. Although this result must be confirmed, this finding could be important among coinfected individuals who are treated with peg-IFN plus RBV, since a low baseline HCV-RNA has a positive influence on SVR rates in these patients [1-4]. In fact, in our study, a well-known predictive factor of better response to peg-IFN plus RBV, as plasma HCV-RNA levels below 600000 IU/mL, was more common among patients taking NVP than in those subjects who were treated with other regimens. Therefore, NVP use might be associated with a higher SVR rate to therapy against HCV infection in HIV/HCV-coinfected patients. In fact, the use of PIs during HCV therapy led to a worse rate of response to peg-IFN plus RBV in the Ribavic clinical trial and in another smaller study [2,8]. Nevertheless, prospective studies are needed to clarify this issue.

The reasons whereby NVP use could be associated with a lower HCV load in HIV/HCV-infected patients is unknown. One possible mechanism might involve the modulation of HCV replication by transforming growth factor (TGF-beta1). In an in vitro model, it has been shown that HIV virions can induce HCV replication through TGF-beta1 [9]. TGF-beta1 is produced in the liver mainly by hepatic stellate cells in response to various signals, such as liver inflammation and tumor necrosis factor alpha (TNF-alpha) [10]. Likewise, NVP has been associated with significantly greater reductions in serum levels of soluble type 2 TNF-alpha receptor (sTNFR2) than other antiretroviral regimens in the long term [11]. Decreases in the TNF-alpha system activity might hypothetically reduce TGF-beta1 secretion in the liver and, in this way, lower HCV replication. However, in vitro studies aimed to explain the underlying mechanism for this finding are needed.

Our study has some limitations. First, the number of patients with NVP was relatively low. This was a study based on real life clinical practice, and NVP is prescribed less commonly than EFV or PIs in HIV/HCV-coinfected patients in our area. Second, the study design was retrospective. This could have led to unnoticed biases. In fact, the length of time with undetectable HIV viral load was greater in the NVP group than in the other two treatment groups. Successful ART is associated with an initial transient increase in HCV-RNA levels followed by a steady decline [12]. In this way, differences in HCV load found in this study could be due to a different duration of undetectable HIV viral load among patients who received NVP, EFV or PIs. However, there was no correlation between the length of time with undetectable HIV viremia and HCV-RNA levels. On the other hand, unfortunately, CD4 cell counts, HIV viral load and HCV viral load at the beginning ART were not available in our study. In this sense, some studies have shown that a low CD4 cell count at starting ART is associated with persistent increases in the HCV viral load [13,14]. Nevertheless, this finding was not observed in a recent study [5].

In conclusion, according to our results, NVP use could be associated with lower HCV-RNA levels among HIV/HCV-infected patients. This finding may have a positive impact on the rate of SVR to peg-IFN plus RBV in these patients. Prospective longitudinal studies are warranted in order to confirm the relationship between NVP and plasma HCV-RNA, as well, the influence of this antiretroviral drug on the SVR rate in HIV/HCV-coinfected individuals.

Acknowledgments

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Table 1: Main features of the three treatment groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NVP group n=24</th>
<th>EFV group n=176</th>
<th>PI group n=160</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>43 (38-46)</td>
<td>42 (38-44)</td>
<td>42 (39-44)</td>
<td>0.5</td>
</tr>
<tr>
<td>Male gender, no. (%)</td>
<td>19 (79)</td>
<td>21 (12)</td>
<td>40 (63)</td>
<td>0.9</td>
</tr>
<tr>
<td>CDC C category, no. (%)</td>
<td>5 (27)</td>
<td>67 (38)</td>
<td>62 (39)</td>
<td>0.6</td>
</tr>
<tr>
<td>Former IUD, no. (%)</td>
<td>20 (85)</td>
<td>140 (85)</td>
<td>139 (87)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hbs Ag positive, no. (%)</td>
<td>17 (71)</td>
<td>119 (68)</td>
<td>102 (64)</td>
<td>0.6</td>
</tr>
<tr>
<td>HCV genotype 1-4, no. (%)</td>
<td>5 (26)</td>
<td>33 (19)</td>
<td>44 (27)</td>
<td>0.6</td>
</tr>
<tr>
<td>Liver fibrosis stage ≥F3, no. (%)</td>
<td>3 (12)</td>
<td>15 (22)</td>
<td>20 (33)</td>
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</tr>
<tr>
<td>Lithium, no. (%)</td>
<td>609 (366-730)</td>
<td>514 (379-660)</td>
<td>483 (515-711)</td>
<td>0.3</td>
</tr>
<tr>
<td>CD4 cell counts (cells/mm3)</td>
<td>23 (96)</td>
<td>157 (89)</td>
<td>141 (88)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Mean (median)*
References


