**HIV-Related Infections, Co-Infections and Cancers – Hepatitis Co-Infection (HCV and HBV) – Part Two**

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*Indicates presenting author.
**BACKGROUND AND OBJECTIVES**

Hepatitis C is a liver disease affecting 170 million people worldwide, which corresponds to 3% of the total population according to the World Health Organization (WHO) [1]. Hepatitis C genotype 1 is the most prevalent genotype in Germany (approximately 60%) [2].

With the protease inhibitors new therapy options have become available in the treatment of chronic hepatitis C (HCV). They are characterized by significantly improved cure rates (sustained virological response, SVR) compared to dual therapy with pegylated interferon plus ribavirin, and a shorter duration of therapy [3]. Also patients without sufficient treatment success under dual therapy (relapser, partial responder, null-responder) show significantly higher cure rates when treated with telaprevir (TVR)-based triple therapy.

The aim of this interim analysis was to evaluate the implementation of futility rules, safety and efficacy of TVR-based therapy in daily practice in Germany.

**METHODS**

In this ongoing prospective, observational, non-interventional, multi-center study, TVR-based triple therapy in therapy-naive and pretreated patients with genotype 1 chronic HCV in Germany is investigated under real-life conditions.

Patients are treated with a combination of telaprevir, ribavirin and peg-interferon. The documentation period covers the entire treatment period and a 24 week post-treatment follow-up period.

Sites were asked to document disease- and treatment-related information as well as HCV-related health care resource consumption. Monitoring visits were performed to verify the data captured against source data. Additionally, electronic data checks on data completeness and consistency were conducted and resulting queries were resolved with the sites.

This interim analysis includes data from the first 100 patients completing 12 weeks of treatment.

**RESULTS**

4 patients were co-infected with HIV. 32 patients were therapy-naive. 66 had received prior treatment against chronic HCV and for 2 patients, the previous treatment status was unknown. Demographic and anamnestic baseline data are presented in table 1.

36.4% of pretreated patients were prior relapser and 30.3% were prior null or partial responder. The median HCV RNA level before initiation of TVR-based therapy was 799,000 IU/ml.

**LITERATURE**

Depressive disorders in HIV/HCV patients undergoing interferon treatment for hepatitis C


ASussex Partnership NHS Foundation Trust, UK. BBrighton and Sussex Medical School, UK. CBrighton and Sussex University Hospitals Trust, UK. DFaculty of Psychology and Educational Sciences of the University of Coimbra, Portugal

Background

Effective clearance rates of HCV with interferon alpha plus ribavirin treatment are reported to be reduced in the co-infected HIV/HCV population when compared to the HCV monoinfected population (Laguno 2004). Neuropsychiatric adverse events are associated with hepatitis C treatment and interferon alpha induced major depressive disorder is commonly reported (Eccles 2012). This study examined the rate and predictors of major depression during interferon alpha plus ribavirin treatment in a Brighton, UK cohort of HCV infected patients including a subsample with HIV coinfection.

Methods

Data was collected from a prospective cohort of HCV infected patients undergoing treatment with interferon alpha plus ribavirin. Study inclusion criteria were age over 18, no previous HCV treatment or prior history of psychiatric illness. Patients with regular injected drug use or alcohol problems, HIV active opportunistic infection, decompensated cirrhosis, and history of neurologic disorders were excluded from the study.

Major depressive disorder was explored at baseline and monthly following treatment initiation using the Structured Clinical Interview for DSM-IV (SCID) criteria and severity assessed with the Hamilton Rating Scale for Depression.

Sustained virological response (SVR) was determined on viral load and defined as HCV RNA <400 IU/mL. Plasma HCV RNA level was measured using a quantitative polymerase chain reaction (PCR) assay. All participants received pegylated interferon alpha plus ribavirin for HIV treatment for up to 12 months. Multiple regression analysis was adopted to explore predictors of later depressive disorders up to 6 months to enable inclusion of all participants treated.

Results

Table 1: Participants characteristics and outcome

<table>
<thead>
<tr>
<th>HIV (n = 188)</th>
<th>HCV (n = 38)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>M (DP)</td>
<td>M (DP)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>45.60 (8.93)</td>
<td>41.14 (9.85)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>71 (37.7)</td>
<td>2 (5.3)</td>
</tr>
<tr>
<td>Male</td>
<td>128 (64.3)</td>
<td>16 (49.7)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/cohabiting</td>
<td>83 (41.7)</td>
<td>11 (28.9)</td>
</tr>
<tr>
<td>Single</td>
<td>59 (49.7)</td>
<td>27 (71.1)</td>
</tr>
<tr>
<td>Separated</td>
<td>13 (6.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Widowed</td>
<td>4 (2.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>100 (52.3)</td>
<td>22 (57.9)</td>
</tr>
<tr>
<td>No</td>
<td>59 (49.7)</td>
<td>16 (41.2)</td>
</tr>
<tr>
<td>Mode of HCV transmission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDU</td>
<td>138 (92.5)</td>
<td>35 (92.1)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (6.5)</td>
<td>3 (7.9)</td>
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</table>

Overall, for most assessment points, only depression HAMD scores assessed at an earlier point stood out as a significant predictor of later major depressive disorder. The exception was depression disorder at week 4, that was significantly predicted by baseline depression HAMD at week 4, that was significantly predicted by baseline depression HAMD scores assessed at an earlier point.

Conclusions

• Our findings show a high prevalence of major depressive disorder during interferon alpha plus ribavirin treatment for both monoinfected and coinfected groups, which is consistent with several studies (Eccles et al, 2012; Schafer et al, 2007; Raison et al, 2005, Laguno et al, 2003).

• Age and gender had no significant effect on major depressive disorder. Only baseline depression predicted major depressive disorder at later time points.

• Lower rates of major depression emergence in this coinfected group may relate to antiretroviral treatment effects.

• Limitations of our study include a small coinfected sample size and the absence of immunological data over the time course.
WHY DON'T WE TREAT CHRONIC HEPATITIS C IN HIV PATIENTS?

Results from a cohort of HIV-HCV coinfected patients from the southeast of Spain

PURPOSE OF THE STUDY
To know the different reasons why we decide not to treat or to delay the antiviral treatment against HCV in HIV coinfected patients.

METHODS
Prospective cohort of HIV and HCV coinfected patients, followed in the Infectious Diseases Department of the Santa Lucía Universitary Hospital (Cartagena, Spain) between 1/12/2011 and 28/02/2012 in which we made transitory elastography. We evaluated the main reasons that moved us to decide not to treat or to delay the antiviral treatment against HCV:
- Social-familiar-laboral reasons
- Neuro-psiquiatric severe diseases
- Patient decision
- Low grade hepatic fibrosis
- Previous failure to Pegylated Interferon (IFN) and Ribavirin (RBV) in no-1 genotype patients
- Delay in the approval of the triple therapy with INF-RBV and a protease inhibitor (Boceprevir or Telaprevir) by the Regional Sanitary Authority
- Active alcohol abuse
- Active diseases that contraindicate the antiviral treatment
- Incomplete study of HCV (VL of HCV, genotype, IL28, abdominal ecography)
- Previous intolerance against IFN-RBV and severe thrombocytopenia (<50 x 10⁹/ L).

SUMMARY OF RESULTS

CONCLUSIONS
- In our cohort of HIV-HCV coinfected patients was decided to delay or not to treat chronic hepatitis C in a significant proportion of subjects.
- The low grade of hepatic fibrosis measured with transitory elastography was the main reason for delaying the HCV antiviral treatment.
- The neuro-psiquiatric disease was the main clinical reason to not treat HCV. The delay of the approval of triple therapy treatment by the Regional Sanitary Authority was the most relevant not clinical reason in our prospective study.
EVALUATION OF THE HIV-HCV COINFECTION STATUS IN A COHORT OF SOUTHEASTERN OF SPAIN

To know the main epidemiological, virological and therapeutic characteristics of HCV infection and the degree of hepatic fibrosis in a cohort of HIV-HCV co-infected patients in the southeastern of Spain.

SUMMARY OF RESULTS

Cohort included 109 patients, 27 females (25%) and 82 males (75%), mean age of 45.8 (SD: 6.2) years and mean time of infection of 18.8 (SD: 5.7) years.

Main route of transmission was: IDUs in 80 patients (91%), 13 (12%) by heterosexual intercourse and 3 (2.8%) in MSM.

No statistically significant differences between the years of evolution of HCV based on the route of transmission (p=0.36).

Genotypic analysis, 55 patients genotype 1a (51%), 13 genotype 1b (13%), 19 genotype 3 (17%) and 9 genotype 4 (8.3%). The median HCV viral load was 868,000 IU/ml (6.15 log_{10}).

Degree of liver fibrosis by transient elastography: 48 (44%) significant fibrosis (F3-F4; > 9.5 Kpascal) 30 (28%) liver cirrhosis (F4; ≥ 14.5 Kpascal).

31 patients (28%) received therapy for HCV: 2 (1.8%) INF non-pegylated, 3 (2.8%) INF non-pegylated + RBV and 25 (23%) INF pegylated + RBV.

Degree of liver fibrosis by transient elastography: 48 (44%) significant fibrosis (F3-F4; > 9.5 Kpascal) 30 (28%) liver cirrhosis (F4; ≥ 14.5 Kpascal).

CONCLUSIONS

In our cohort, the gender predominant was male and the abuse of intravenous drugs was the main cause of HCV transmission.

Most patients had genotype 1a, high viral load (>800,000 IU/ml) and a poor rate of SVR (19.3%), predominating the partial response rate among non-responders.

A high proportion of patients (28%) had liver cirrhosis (F4), of which, a significant proportion of subjects (37%) were at high risk of hepatic decompensation (> 40 Kpascal).

6 cases (19%) achieved sustained viral response (SVR). In 25 cases without SVR (81%), 9 (36%) partial responders, 7 (28%) null responders, 6 (24%) relapers and 3 (12%) discontinued treatment.
Insights on treatment of a Portuguese cohort of HCV/HIV coinfected patients

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BACKGROUND

In the era of effective antiretroviral therapy, HCV infection has emerged as a major cause of morbidity and mortality worldwide, development of cirrhosis, and death.

Treatment with peginterferon (PEG-IFN) plus ribavirin (RBV) has been recommended for coinfected patients who are at greatest risk for liver disease; however, toxicity is considerable, and the effectiveness of HCV treatment in this population has been disappointing. Although direct-acting antivirals (DAA), telaprevir and boceprevir, might overcome factors such as immunodeficiency that can reduce the efficacy of PEG-IFN, the potential for interactions between different drugs, additive drug toxicities, the need for therapy with PEG-IFN and the current economic situation, still impose a challenge in HIV/HCV coinfected patients. It’s fundamental to define individual strategies leading to a successful virological response.

PURPOSE OF THE STUDY

Characterize a Portuguese patient population with chronic HCV and HIV coinfection, followed at our research unit, underline the importance of early treatment and incorporate the importance of DDA for retreatment of HCV infection.

METHODS

Retrospective, observational analysis of medical records related to 348 HCV/HIV coinfected patients. Description of demographic, epidemiological, clinical and laboratory data, identification of causes related with HCV treatment delay and virologic response in those who were treated.

RESULTS I

n=348
patients HIV/HVC+

HCV Treatment Initiation

n = 121

CHARACTERIZATION

• SEX: 77,0% male
• AGE: average of 44 yo; [25; 77 yo]
• RACE: 94.8% Caucasian
• ROUTE OF HCV INFECTION:
  71.3% IDU and 8.3% MSM
• FREQUENT MORBIDITIES:
  Alcohol abuse 46.8%
  IDU 70.1%
  Methadone 25.6%
  Mental Disturbances 12.3%

RESULTS II

HIV INFECTION

• HCV - 1 n= 342; HCV-2 n=6.
• Average time since diagnosis was 11 Yrs.
• CDC Atlanta Stage:

Among the 121 patients on HCV treatment:

• Viral load before HCV treatment: 76.9% with indetectable VL (n=93)
• TCD4 count before HCV treatment: 9.9% ≤ 200 TCD4 cells (n=12)
• On antiretroviral treatment: 94.8%

RESULTS III

DISEASE STAGE PREVIOUS TO TREATMENT

• BASELINE HCV ARN
  ≥ 600 000 UI/ml in 56.9%
• BASELINE ALT
  > 2 times the limit in 38.0%, Average 94 UI/ml
• FIBROSIS:
  Fibroelastography in 41.1 %;
  Hepatic biopsy in 26.3%;
  > F2 METAVIR in 44%.
• IL28B was performed in only 35 patients at the time.

HCV TREATMENT in 34.8% patients (n=121)

1.7 treatments/ patient.
Peginterferon plus Ribavirin in 93.6%

SVR rate - 51.2%;
Non Responders - 28.9%;
Relapsers - 3 patients;
Treatment Interruptions on 9 patients.

CONCLUSIONS

1. Our data presents a low HCV treatment initiation rate, illustrated by 34.8% of HCV/HIV patients who began therapy.
2. The majority of patients completed treatment and the SVR rate although insufficient was similar to those reported in literature.
3. Individualized approach is essential to determine the optimal time to initiate HCV treatment, to assess patient motivation, adverse events management and facilitate adherence, in order to achieve a successful treatment and reserve DDA treatment to experienced patients with worse predictive factors.

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Editorial points

- The efficacy and safety of treatment of chronic hepatitis C (HCV) with pegylated interferon (PegIFN) and ribavirin (RBV) has been extensively studied. The use of PegIFN and RBV has been associated with a significant reduction in the rate of relapse and failure of treatment.

- The results of the study indicate that the treatment of chronic hepatitis C with PegIFN and RBV is effective and safe. The study also highlights the importance of monitoring ALT levels during therapy as a predictor of treatment outcome.

- The study findings support the use of PegIFN and RBV as the standard of care for the treatment of chronic hepatitis C. The results also suggest that the use of EFV as part of the ART regimen may lead to increased SVO rates among group 1 patients.
Hepatotoxicity of antiretrovirals in patients with human immunodeficiency virus and viral hepatitis coinfections

Authors: Lupo S, Parenti P, Marconi L.
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Department of AIDS
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Background:
• Antiretroviral drugs used to treat HIV may cause hepatotoxicity. The high prevalence of persons with chronic hepatitis B or C coinfected, raised aminotransferases have many causes and neither specific markers is a indicator of liver injury, difficulties in interpreting the hepatotoxicity.
• Objective: We evaluated hepatotoxicity in HIV/HVC and/or HBV coinfected patients, risk factors and severity.

Methods:
• Prospective study of HIV-1 patients with start HAART in Hospital Provincial del Centenario from Rosario, Argentina.
• Patients were classified into two groups, VHC and/or VHB coinfected vs. no coinfected.
• The mayor endpoint was hepatotoxicity defined as Benichou’s Score within de first 6 months. This score is among the few validated, but little used in clinical practice.
• Secondary endpoints were risk factors and severity of hepatotoxicity.

Results:
• 140 patients were included, 39% coinfected and 61% no coinfected.
• Female were similary in both groups 21% and 27% respectively.
• The hepatotoxicity within the first 6 month was 44.3%, 75% in coinfected patients and 25 % in no coinfected. RR 3.97 (IC95% 2.34-6.75, p<0.0001).
• The hepatotoxicity was associated with the use of illicit drugs and alcohol, symptoms, high level aminotransferases previous to HAART and NRTI+PI.
• 3% of hepatotoxicity was severe.

Conclusions:
• 44% of HIV patients experienced hepatotoxicity, 75% in coinfected vs 25% in no coinfected.
• The RR of hepatotoxicity was almost 4 times higher among in chronic hepatitis coinfection patients, compared with those with HIV non-coinfected.
• In multivariate analysis, the risk factors were illicit drugs, alcohol, symptoms, high level aminotransferases and NRTI+PI.
• Only 3% of hepatotoxicity was severe.
• The Benichou’s Score is better than level of aminotransferase for evaluated hepatotoxicity, so it would recommended for use in clinical practice.

Bibliography

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Sexually transmitted infection with an immune-escape mutant hepatitis B virus (HBV) in an HBV-vaccinated individual with acute HIV-HCV infection

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Introduction

Chronic hepatitis B virus infection is a global pandemic affecting around 400 million individuals worldwide. Hepatitis viruses account for 57% of cirrhosis and 78% of hepatocellular carcinoma (HCC) globally and cause one million deaths each year.

HIV co-infected subjects with HBV and/or HCV are at increased risk of cirrhosis and HCC. Of the 33 million HIV infected subjects worldwide, 5-25% are co-infected with HBV (2-4 million) and/or HCV (4-5 million), and viral hepatitis has become one of the major causes of morbidity and mortality in HIV-infected individuals in the Western world. Since 1982, an effective vaccine against HBV is available!

Immune pressure exerted on the hepatitis B virus (HBV) by anti-HBV antibodies and long-term therapy with drugs that mutagenize the viral polymerase gene can select for mutations in its surface gene, possibly leading to vaccine escape and evasion from serological detection. In general, these mutations are considered poorly transmissible.

However, cases of HBV infection with vaccine-escape mutant viruses have been reported in vaccinated individuals, mainly from high-prevalence regions of the world.

Here, we report a case of a HBV vaccine escape mutant infection in an effectively vaccinated individual:

Case Report

The patient was a 27-year old Italian men who has sex with men (MSM) who presented in September 2011 for the first time in our Berlin outpatient HIV clinic due to a newly diagnosed HIV infection. He was aware of several sexual high-risk contacts within the past, but had a documented negative HIV and HCV antibody test (ELISA) in April 2011. He complained about slight fever, swollen cervical and axillary lymph nodes and general muscle pain.

The HIV infection was confirmed by Western Blot, moreover an acute HCV infection was confirmed (positive HCV RNA, ALT 10x the upper limit of normal (ULN)). He was effectively vaccinated against HBV in the past. The lab results at initial presentation are shown in table 1.

Three months later, the patient was routinely retested.

This time, his HBsAg turned out to be positive, and his anti-HBs antibodies had vanished. His HBV viral load was 606 mio iU/mL.

Population sequencing of the HBV genome revealed an HBV genotype F and a S143L mutation in the surface gene consistent with a vaccine escape mutant virus. The patient was started on an antiviral regimen consisting of tenofovir/emtricitabine and boosted darunavir.

Table 1: Laboratory results at initial presentation

<table>
<thead>
<tr>
<th>Lab parameter</th>
<th>Result</th>
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<tbody>
<tr>
<td>CD 4 cell count [%] [mm³]</td>
<td>529 (26)</td>
</tr>
<tr>
<td>HIV viral load [copies/mL]</td>
<td>26,400</td>
</tr>
<tr>
<td>ALT [U/L]</td>
<td>512</td>
</tr>
<tr>
<td>AST [U/L]</td>
<td>204</td>
</tr>
<tr>
<td>HCV viral load [iU/mL]</td>
<td>2.1mio</td>
</tr>
<tr>
<td>HCV genotype</td>
<td>2c</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-HBs [iU/L]</td>
<td>121</td>
</tr>
</tbody>
</table>

Conclusions

To our knowledge, this is the first case of sexual HBV transmission in an effectively vaccinated individual

This is the first documentation of a sexual transmission of a HCV genotype 2 in HIV-positive MSM in Europe

Clinicians need to be aware of vaccine-escape mutant HBV trasmission