Poster Q-176

CROI 2009

# Hyaluronic Acid as a Prognostic Marker of Hepatic Encephalopathy and Liver-related Death in HIV/Viral Hepatitis Coinfected Patients


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## INTRODUCTION

There is a lack of studies of biomarkers predicting risk of liver-related events (LRE; hepatic encephalopathy or liver-related death) in HIV-infected persons also infected with hepatitis B and/or hepatitis C virus.

## OBJECTIVES

To investigate plasma hyaluronic acid (HA) as a prognostic marker for LRE in HIV/viral hepatitis coinfected patients within the EuroSIDA study

## METHODS

### Patients

1377 HIV-1 infected patients were included. Of them were 1309 positive for HBsAg (denoted HBV) and/or anti-HCV (denoted HCV). A control group of 68 HIV-monoinfected patients were also included, table 1.

All hepatitis coinfected patients had to have least one plasma sample available after being diagnosed anti-HCV and/or HBsAg positive.

### Study end points

The primary end point was the composite of liver-related death (LRD) or the development of hepatic encephalopathy, while secondary end points were non-liver-related death and development of AIDS.

Deaths were classified as "liver-related" if clinical or autopsy diagnoses described either liver failure, chronic viral hepatitis, peritonitis, hepatocellular carcinoma, hepatic encephalopathy, oesophageal bleeding, other gastro intestinal bleeding in the presence of cirrhosis/end-stage liver disease, liver failure in the presence of acute bacterial infection in patients with previously known end-stage liver disease or medication-related hepatotoxicity resulting in hepatic failure.

Hepatic encephalopathy was defined as grade 3 or 4 based on the West Haven Criteria of Altered Mental Status In Hepatic Encephalopathy (Ferenci et al; Hepatology 2002).

### Hyaluronic acid

Quantitative determination of HA in stored plasma samples was performed in the first available plasma sample after being tested positive for anti-HCV and/or HBsAg using a commercial enzyme linked binding protein assay (Corgenix, Colorado, USA) with a HA range in a healthy population between 0-75 ng/mL. Each HA level was measured in duplicate.

All patients that developed a LRE during follow-up had HA measured in their last available sample prior to their event. As a control group, a random selection of one sixth of the remaining patients also had HA measured in their last available plasma sample.

### Statistical methods

Kaplan-Meier estimation was used to estimate the probability of any LRE in different strata. Poisson regression was used to determine the factors associated with the development of primary and secondary end points. For all analyses, patient follow-up began at the date of HA measurement and ended at the development of an event or last follow-up.

Table 1

**Baseline characteristics of 1377 patients**

| | | % |
|---|---|---|
| Gender | Male / Female | 73.0 / 27.0 |
| Exposure | MSM / Hetero/ IDU/ Other | 22.6 / 55.5 / 13.1/ 8.8 |
| HBV / HCV | - / + | 68.1 |
| - | + / - | 17.8 |
| - | + / + | 9.1 |
| - | - / - | 5.0 |
| | | Median (IQR) |
| Age (years) | | 38.2 (33.3 – 43.2) |
| CD4 (cells/µl) | | 342 (210 – 504) |
| HA date | | 5/00 (7/98 – 3/03) |

Figure 1

**Kaplan Meier progression to any liver-related event**

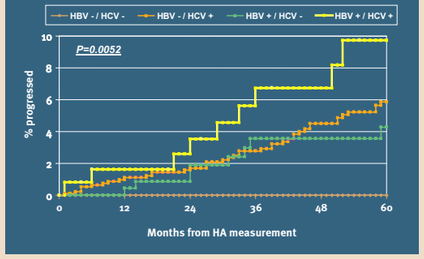



Figure 2

**Distribution of HA and any liver-related events**

## RESULTS

### Baseline HA and risk of clinical progression

The baseline characteristics of the 1377 included patients are shown in **table 1**. The median baseline HA level for all patients was 32.9 ng/mL (interquartile range [IQR] 17.4 - 65.5). Median HA (IQR) for the four patient groups (HBV-/HCV+, HBV+/HCV-, HBV+/HCV-, HBV-/HCV-) was 34.3 (18.3 - 70.3), 29.4 (16.6 - 56.9), 33.1 (19.3 - 90.4) and 19.5 (11.9 - 38.2), respectively.

During a median follow-up of 4.9 years (IQR 2.8 - 7.6 years) 68 (4.9%; 44 LRD and 24 hepatic encephalopathy) patients developed a liver-related event (LRE). Patients positive for both HBV and HCV progressed fastest to a LRE, while none of the HIV monoinfected patients experienced an event, **figure 1**.

For patients who developed a LRE during follow-up the median HA was 247.1 ng/mL (IQR 116.7-618.9), while it was 31.2 ng/mL (IQR 16.8 – 61.1) for patients who did not experience a LRE. **Figure 2** shows the distribution of HA for all patients divided in to deciles; the proportion of patients experiencing any LRE was low with low HA. 57 (83.8%) events occurred with a baseline HA >146.8 ng/mL, while only one out of 551 with a baseline HA <25.7 ng/mL experienced an event. **Figure 3** shows a Kaplan-Meier plot for any LRE using the median HA (250 ng/mL) for stratification. Having a baseline HA of less than 250 ng/mL resulted in a cumulative 5 year risk of experiencing a LRE of 3.0%, while the 5 year risk was 43.6% for patients with a baseline HA higher than 250 ng/mL. For HA ≥ 75 vs. < 75 ng/mL the corresponding 5 year risks of experiencing a LRE were 21.7% and 0.86%.

### HA as predictor of development of clinical events

The multivariate incidence rates ratios (IRR) for any LRE are shown in **figure 4.** HA (≥ 250 vs. < 250 ng/mL) was by far the strongest predictor of any LRE with an IRR of 15.17 (IQR 8.94 –25.75, p<0.0001).

For the development of AIDS and non-liver-related death the IRR for HA (≥ 250 vs. < 250) was 0.83 (IQR 0.38 – 1.85, p=0.65) and 1.63 (IQR 0.91 – 2.93, p=0.10), respectively.

### HA at follow-up

48 (70.6%) patients that developed a LRE during follow-up had HA measured in their last available sample prior to their event (cases). 194 (14.8%) patients were included as controls.

25 (52.1%) of the cases had an increase in HA of more than 100 ng/mL, while 12 (25%) had decreasing HA. 6 cases had a HA <75 ng/mL at follow-up, one of them decreasing from a HA higher than 250 ng/mL at baseline. Of the controls only 10 (5.2%) had an increase in HA of more than 100 ng/mL, while 81 (41.8%) had decreasing HA. 12 (6.2%) controls had a HA >250 ng/mL at follow-up.

For the cases the median change in HA per year was 103.5 ng/mL (IQR –7.4 to 212.0), while it was 1.06 ng/mL (IQR –4.75 to 8.27) for the controls, p<0.0001 for comparing the median annual change.

As change in HA was not normally distributed, we used logistic regression to look at odds of ≥1 standard deviation (SD) (189 ng/mL) increase in HA. In the univariate analysis cases had a 11-fold increased odds of ≥1 SD in HA (odds ratio [OR] 11.0, 95% confidence interval [CI] 4.14 – 29.25, p<0.0001). In multivariate analysis, predictors of ≥1 SD change in HA were CD4 (per doubling) (OR 0.64, 95% CI 0.44 – 0.92, p=0.015) and being a case (OR 8.58, 96% CI 3.13 – 23.53, p<0.0001).

## SUMMARY AND CONCLUSIONS

- Baseline HA level was a very strong predictor of later development hepatic encephalopathy or liver-related death in HIV-1 patients coinfected with HBV and/or HCV
- Patients, who during follow-up experienced a liver-related event, had higher annual increase in HA compared to patients without an event
- A high CD4 cell count reduced the risk of increasing HA, consistent with the assumed protective role of high CD4 cell counts on the risk of LRE in coinfected patients
- Therefore, plasma HA may be useful, either alone or in combination with other non-invasive methods to monitor progression of liver disease in patients with chronic viral hepatitis

Figure 3

**Kaplan Meier progression to any liver-related event**

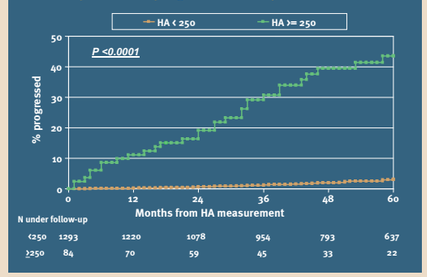
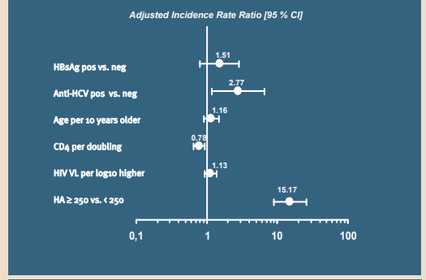



Figure 4

**Risk of any liver-related event**





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