IS LIVER DISEASE A THING OF THE PAST?

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Liver disease in haemophilia

- Liver disease is one of the main co-morbidities in adult patients with haemophilia

- Liver disease in haemophilia is almost exclusively due to blood-borne viral infections (HCV, HBV, HCV/HIV)

- Patients treated before 1986 with large-pool clotting factor concentrates had a near 100% risk of infection with non-A non-B virus

- In the HAART era liver disease and liver cancer represents the first cause of mortality in adult patients with haemophilia after bleeding

HCV, hepatitis C virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy

References:
Arnold et al Blood 2006; 108: 460-4

Fletcher et al BMJ 1983; 287: 1754-7
Kernoff et al Br J Haematol 1985; 60: 469-79
Chronic hepatitis C – natural history

Acute infection

Self-limited infection – 15-30%

Chronic infection – 70-85%

Chronic Hepatitis

Mild

Moderate

Severe

Cirrhosis – 20-30%

ESLD

HCC – 4%

Death – 4%

ESLD, end stage liver disease; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation

Adapted from Hoofnagle JH Hepatology 1997;26(suppl 1):15–20S
Natural history of hepatitis C in haemophilia – age at infection

- In the mid-1980s: HIV-related deaths
- In the HAART era: reduced HIV-related as well as liver-related mortality
- ESLD and HCC: long-term sequelae in survivors
- HIV co-infection is the most important predictor of ESLD/HCC

- Mortality related to liver disease was 16.7 times higher than in the general population
- Mortality related to liver cancer was 5.6 times higher

HAART, highly active antiretroviral therapy; ESLD, end stage liver disease; HCC, hepatocellular carcinoma; HIV; human immunodeficiency virus
Natural history of hepatitis C in haemophilia – age and coinfections

- During the AIDS epidemic liver–related mortality was “artificially” lower
- In the HAART era ESLD became the leading cause of death

- With HIV coinfection the annual hazard of ESLD increased over time for patients with chronic HBV infection (cumulative incidence rate: 30.1%)
- ESLD risk was increased by 2.1 folds in patients with <200/mmC CD4+Ly

AIDS, acquired immune deficiency; HAART, highly active antiretroviral therapy; ESLD, end stage liver disease; HBV, hepatitis B virus; HIV, human immunodeficiency virus

Goedert et al Blood 2002; 100: 1584–9
Quintana et al Haemophilia 2003; 9: 605–12
Natural history of hepatitis C in haemophilia – disease duration

- 847 patients; 687 (81%) with chronic hepatitis; 210 (25%) HIV coinfected
- Median disease duration: 27 yrs
- 71 pts developed ESLD after 21 yrs

- 59 had liver failure
- 13 HCC
- 55 died for liver disease
- 9 underwent OLT

ESLD, end stage liver disease; HCC, hepatocellular carcinoma; HIV; human immunodeficiency virus
Natural history of hepatitis C – the impact of HAART and antiviral therapy

- **Overall survival**
  - Duration of HCV infection (yr)
  - Proportion remaining ESLD-free
  - Time since HCV infection (yr)
  - Duration of HCV infection (year)

- **Eradication after antiviral therapy**

- **Chronic infection, untreated**

- **HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV; human immunodeficiency virus**

Van de Putte et al J Hepatol 2014; 60: 39–45
Ragni et al Haemophilia 2009; 15: 552–8
The evolution of HCV therapy

HCV, hepatitis C virus; IFN, interferon; PEG, pegylated; RBV, ribavirin; DAA, direct-acting antiviral; SVR, sustained virological response

Modified from Strader et al Hepatology 2004; 39: 1147–71
IFN–based therapy – results

• SVR achieved in*:

- 40–54% of pts with HCV type 1 treated with SOC for 48 w
- 65–82% of pts with HCV type 2 or 3 treated with SOC for 24 w
- 17–36% of pts with HCV type 1 and HIV co-infection
- 44–72% of pts with HCV type 2 or 3 and HIV co-infection

* all patients

HCV, hepatitis C virus; SVR, sustained virological response; SOC, standard of care; HIV, human immunodeficiency virus
IFN–based therapy – results in pts with haemophilia

• Overall, SVR achieved in:
  - 45–70% of patients infected only with HCV treated with SOC for 24 or 48 weeks depending on HCV type (30–50% G1; 84–86% G2 or 3)
  - 22–48% of patients co–infected with HIV treated with SOC for 48 weeks irrespective of HCV type (37% G1; 60% G2 or 3)

Patients with haemophilia have the same predictors of SVR

IFN, interferon; HCV, hepatitis C virus; SVR, sustained virological response; SOC, standard of care; HIV, human immunodeficiency virus
Direct antiviral agents

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>GT2</th>
<th>GT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF + RBV 12w</td>
<td>97%</td>
<td>96%</td>
</tr>
<tr>
<td>SOF + DCV 12w</td>
<td>94%</td>
<td>97%</td>
</tr>
</tbody>
</table>

**SVR12 (%)**

- **Overall**
  - Naive: 90%
  - Experienced: 97%
- **Non-cirrhotic**
  - Naive: 97%
  - Experienced: 100%
- **Cirrhotic**
  - Naive: 78%
  - Experienced: 97%

**Direct antiviral agents**

- **SOF**, sofosbuvir
- **RBV**, ribavirin
- **GT**, genotype
- **DCV**, daclatasvir
- **SVR**, sustained virological response
- **LDV**, ledipasvir

**References**

The impact of DAA on long-term outcomes

- The high efficacy of DAA is related both to mechanism of action and rapidity of viral clearance (RVR was the best predictor of SVR)

- SVR is related to decrease of mortality, lower risk of HCC, need for OLT, reduction of extrahepatic diseases associated with HCV infection

- All 3 classes have high potency

- Only SOF has a high genetic barrier which is important to avoid viral drug resistance

DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; RVR, rapid virological response; SVR, sustained virological response; OLT, orthotopic liver transplantation; SOF, sofosbuvir, RNA, ribonucleic acid

Courtesy of Dr Aghemo
Hepatocellular carcinoma in haemophilia

- HCC is the leading cause of death in patients with HCV-related cirrhosis
- Risk factors: old age, male gender, heavy alcohol intake, HBV or HIV coinfections

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients who developed HCC (n=6)</th>
<th>Patients who did not develop HCC (n=379)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>61 (45–70)</td>
<td>31 (10–81)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>6 (100%)</td>
<td>34 (9%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Baseline AFP (ng/mL)</td>
<td>25 (7–42)</td>
<td>4 (1–88)</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>Months of infection</td>
<td>250 (156–336)</td>
<td>239 (120–588)</td>
<td>&lt;.7</td>
</tr>
<tr>
<td>Anti-HIV</td>
<td>1 (16%)</td>
<td>140 (37%)</td>
<td>&lt;.3</td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>4 (67%)</td>
<td>307 (81%)</td>
<td></td>
</tr>
<tr>
<td>Haemophilia B</td>
<td>1 (16%)</td>
<td>59 (16%)</td>
<td>&lt;.2</td>
</tr>
<tr>
<td>vWd</td>
<td>1 (16%)</td>
<td>13 (3%)</td>
<td></td>
</tr>
</tbody>
</table>

385 pts; HCC incidence rate 0.39% per year; f_up: 4 years

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, older than 62 y</td>
<td>7.3 (1.4–38.2)</td>
<td>1.8 (0.1–36.9)</td>
</tr>
<tr>
<td>Age at HCV infection, older than 40 y</td>
<td>6.9 (1.3–35.9)</td>
<td>3.4 (0.2–69.9)</td>
</tr>
<tr>
<td>AFP level at entry, higher than 11 ng/mL</td>
<td>11.6 (2.6–51.5)</td>
<td>15.2 (2.7–85.7)</td>
</tr>
<tr>
<td>ALT level at entry, higher than 176 IU.L</td>
<td>1.3 (0.1–10.7)</td>
<td>1.2 (0.1–11.8)</td>
</tr>
<tr>
<td>Alcohol intake, more than 80 g/d</td>
<td>8.8 (2.0–38.5)</td>
<td>12.9 (2.4–68.7)</td>
</tr>
</tbody>
</table>

559 pts; HCC incidence rate 0.24% per year; f_up: 6 years

- In patients with cirrhosis the rate of HCC development is 3–6% per year
- 6–month surveillance group: 2.4% cumulative incidence; 0.4% incidence rate
- 12–month surveillance group: 0.9% cumulative incidence; 0.1% incidence rate
- In patients with haemophilia often HCC are multinodular upon diagnosis

HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; HIV; human immunodeficiency virus

Santagostino et al Blood 2003; 102: 78–82
Hepatocellular carcinoma in haemophilia – diagnosis and staging

- Active surveillance is warranted in order to make early diagnosis and treat
- US examination every 6 months and regular AFP assessment: mortality reduction of 37%
- US sensitivity threshold is 2cm; CT and MRI scan have higher sensitivity
- In NON-cirrhotic pts who achieved SVR surveillance is no longer required
- Symptoms occur only at advanced stages

<table>
<thead>
<tr>
<th>Diagnostic criteria for HCC</th>
<th>The Barcelona Clinic Liver Cancer (BCLC) staging system</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cyto–histological criteria</strong></td>
<td>HCC</td>
</tr>
<tr>
<td><strong>Non–invasive criteria (restricted to cirrhotic patients)</strong></td>
<td></td>
</tr>
<tr>
<td>1. Radiological criteria: two coincident imaging techniques&lt;sup&gt;a&lt;/sup&gt;</td>
<td>O, very early stage</td>
</tr>
<tr>
<td>Focal lesion &gt;2 cm with arterial hypervascularization</td>
<td>A, early stage</td>
</tr>
<tr>
<td>2. Combined criteria: one imaging technique associated with AFP</td>
<td>B, intermediate stage</td>
</tr>
<tr>
<td>Focal lesion &gt;2 cm with arterial hypervascularization</td>
<td>C, advanced stage</td>
</tr>
<tr>
<td>AFP levels &gt;400 ng/ml</td>
<td>D, end stage</td>
</tr>
</tbody>
</table>

<sup>a</sup>Four techniques considered: US, spiral CT, MRI and angiography

US, ultrasound; AFP, alpha–fetoprotein; CT, chromatography; MRI, magnetic resonance imaging; SVR, sustained virological response

Surgical resection:
- Single HCC + normal liver function + absent portal hypertension
- Recurrence rate: 70% at 5 yrs

Interstitial treatments:
- Percutaneous ethanol injection:
  - Small (≤ 3 cm) nodules (< 3)
  - 80% CR
  - 50% CR if 3-5 cm
- Radio-frequency thermal destruction:
  - Small (≤ 3 cm) nodules (< 3)
  - Better results with fewer sessions but with higher rate of side effects; problems with tumour location
- Chemoembolization:
  - Multinodular, intermediate stage
  - With either chemotherapeutic drugs or microbeads

OLT:
- Milano criteria
- 5-year survival: 73%
- Organ availability

Sorafenib:
- Advanced stage
- Survival advantage: 3 mos

HCC, hepatocellular carcinoma; CR, complete response; OLT, orthotopic liver transplantation

*curative treatments
Liver transplantation – general aspects

- Worldwide >50% of OLT are needed for ESLD or HCC related to chronic HCV infection
- In patients with haemophilia OLT cures also the coagulation defect
- HCV recurrence is universal after OLT candidates should receive DAA
- The Milano criteria apply also to haemophilia patients; haemophilia does not represent an additional criterion
  - one lesion \( \leq 5 \) cm
  - \( \leq 3 \) nodules \( \leq 3 \) cm
  - no gross vascular invasion, no regional nodes or distant metastases
- Livers are allocated based on the MELD score (bilirubin, creatinine, INR)
- Patient with HCC are given 22 MELD points
- The first successful OLT in haemophilia was performed in 1985

ESLD, end stage liver disease; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; HCV, hepatitis C virus; DAA, direct-acting antiviral; MELD, model for end stage liver disease; INR, international normalised ratio
Liver transplantation in haemophilia

1985-1996

HIV- (n=20)
- Median age: 46 yrs
- HCV ESLD in 69%
- Time to normal coag: 24h
- Time to HCV recurr: 9 mos

HIV+ (n=6)
- Median age: 52 yrs
- HCV ESLD in 78%
- Time to normal coag: 72h
- 5-yr survival: 53.5%

1994-2008

HIV- (n=13)
- Median age: 52 yrs
- HCV ESLD in 78%
- Time to normal coag: 72h

HIV+ (n=5)

ESLD, end stage liver disease; HCV, hepatitis C virus; HIV, human immunodeficiency virus

Pan-EMEA Haematology Exchange Forum

Liver transplantation in haemophilia

(a) 100%

% Alive

0.0 0.5 1.0 1.5 2.0 2.5 3.0

Years post-transplant

P=0.64

n=27

Non-haemophilic

Haemophilic

(b) 100%

% graft functioning

0.0 0.5 1.0 1.5 2.0 2.5 3.0

Years post-transplant

P=0.80

n=62

Non-haemophilic

Haemophilic

(c) 100%

% rejection

0.0 0.5 1.0 1.5 2.0 2.5 3.0

Years post-transplant

P=0.77

Non-haemophilic

Haemophilic

(a) 100%

% Alive

0.0 0.5 1.0 1.5 2.0 2.5 3.0

Years on transplant waiting list

P=0.03

n=8

Non-haemophilic

Haemophilic

(b) 100%

% not transplanted

0.0 0.5 1.0 1.5 2.0 2.5 3.0

Years on transplant waiting list

P=0.15

n=7

Non-haemophilic

Haemophilic

(c) 100%

% with MELD <25

0.0 0.5 1.0 1.5 2.0 2.5 3.0

Years on transplant waiting list

P=0.06

Non-haemophilic

Haemophilic

2003–2010

Ragni et al Haemophilia 2013; 19: 134–40
Liver transplantation in haemophilia

HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus
How to assess liver disease

• The gold standard technique to assess the presence of chronic hepatitis and/or liver fibrosis is \textit{liver biopsy}.

• Cirrhosis can be evident with ultrasound but the most well-tested non-invasive technique is \textit{liver elastography} (FibroScan) an ultrasound-based technique to measure liver stiffness with 64% sensitivity for F2–4 fibrosis and 86% for cirrhosis.
## How to monitor liver disease

<table>
<thead>
<tr>
<th>Chronic infection</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of cirrhosis</td>
<td>Every 3 months</td>
</tr>
<tr>
<td>Lab assessment for liver function</td>
<td>Lab assessment for liver function</td>
</tr>
<tr>
<td>US/FibroScan exam.</td>
<td>US examination</td>
</tr>
<tr>
<td>US/FibroScan exam.</td>
<td>Every 12 months</td>
</tr>
<tr>
<td>US/FibroScan exam.</td>
<td>EGD examination</td>
</tr>
<tr>
<td>US/FibroScan exam.</td>
<td>Every 24 months</td>
</tr>
</tbody>
</table>

US, ultrasound; EGD, esophagogastroduodenoscopy
Conclusions

- HCV infection and its long-term complications represent the main cause of morbidity and mortality in adult patients with haemophilia.
- Liver disease has to be regularly assessed and followed-up.
- Active surveillance is crucial to treat HCC.
- All infected patients should undergo antiviral therapy with DAA, however cost is an issue.
- OLT is a reasonable option for patients with haemophilia but requires treatment of infection to prevent recurrence.

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; DAA, direct-acting antiviral; OLT, orthotopic liver transplantation.
Q&A SESSION
Please complete the evaluation form