Hepatology Highlights
for the HIV physician

What’s new in non-viral liver disease

London
June, 15th, 2016

Patrick Ingiliz, Berlin
Conflicts of interest

• Consultancy or speakers fees from abbVie, BMS, Gilead, Janssen, MSD, Roche, ViiV.

• Clinical trials with abbVie, Gilead, BMS, ViiV, Hologic, Janssen, MSD, Boehringer-Ingelheim.
Klaus, 51yo

- caucasian, MSM
- HIV infection, dx 1989, CDC B2
- presents for chronic ALT elevation:
  - “since ages“
Klaus, medical history

- varicose veins
- PVD (femoro-popliteal bypass)
- hyperlipoproteinemia
- hyperuricemia

→ Meds: ASS, allopurinol
Klaus, ARV history

- 1997-2000: AZT, 3TC
- 2000-2002: 3TC, d4T
- 2002-2003: 3TC, d4T, EFV
- 2003-2011: TDF, 3TC, LPV/r (diarrhea)
- 2011-2012: TDF/FTC/ATV/r (LEE)
- 2012-2012: TDF/FTC/RPV (HIV-VL)
- since 2012: TDF/FTC/RAL
Klaus, 51yo

- 1,99m, 97kg, BMI 24,5 kg/m²
- RR 110/60
- hip circumference: 101cm
- waist circumference 98cm
- ex-smoker

- physical exam: lipodystrophy syndrome
Klaus, lab results

- CD4 475/μl, 40%
- HIV <50 c/ml
- AST 85 U/L, ALT 93 U/L, GGT 123 U/L
- Thr 116 G/l
- Alb, Bili, INR within normal range
- TG 234mg/dL, Chol 143mg/dL, HDL 31mg/dL
- Glucose 111mg/dL
Klaus, hepatopathy screening

- HBV: vaccinated
- HAV, HCV negative
- HEV: IgG positive, PCR negative
- No sign of autoimmune or hereditary liver disease

- US abd.: dense liver parenchyma suggesting steatosis, pancreas lipomatosis, spleen 19cm
Klaus, liver staging

- Fibroscan 23.9 kPa (IQR 3.1, SR 91%)
- CAP® 278 dB/m
• MRI (ECHAM trial): steatosis 6%

• Liver biopsy: 39mm, 25 portal tracts:
  • steatosis ° I, hepatocytic ballooning, slight lobular inflammation. (NAS-Score 4)

• Fibrosis stage: F3 (partly F4) METAVIR
Chronic ALT elevation in HIV monoinfection

2365 participants, 9972 person-years: incidence rate 3.9/100py

16%
Swiss cohort
Chronic ALT
No HCV/HBV

(high BMI, alcohol, HIV viral load > 100,000 c/mL, stavudine/zidovudine)
Causes of cirrhosis in HIV patients

2,168 HIV patients
Cross sectional analysis
*Transient elastography* (TE, Fibroscan)

181/2168 (8.3%) with TE ≥ 12 kPa

No cirrhosis attributable to alcohol alone

**Fig. 1** Aetiology of liver cirrhosis in the HIV study population.
US HIV positive veteran registry: n=24,040

Prevalence of cirrhosis in 2009: 5%

<table>
<thead>
<tr>
<th>Non viral independent variables</th>
<th>Compensated cirrhosis n=1190</th>
<th>Decompensated cirrhosis n=565</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (1.02-1.04)</td>
<td>1.02 (1.01-1.03)</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>1.76 (1.4-2.2)</td>
<td>1.96 (1.51-2.54)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.79 (1.6-2.1)</td>
<td>1.91 (1.59-2.31)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>1.78 (1.5-2.1)</td>
<td>1.65 (1.32-2.08)</td>
</tr>
</tbody>
</table>
Non-viral chronic liver diseases in HIV patients

Antiretroviral therapy (ART)

Vascular liver disease

Alcohol abuse
Metabolic disorders
Antiretroviral therapy (ART)

Steatohepatitis +/- fibrosis
Nodular Regenerative Hyperplasia (NRH)

Main cause in non HIV:
Thrombophilia
Protein C deficiency,
Factor V Leiden…. 

Arteritis with secondary portal vein thrombosis 
Obstructive Portal Venopathy 

Inferior vena cava
Gall bladder
Portal vein
Common bile duct
Hepatic artery
Nodular regenerative hyperplasia is a new cause of chronic liver disease in HIV-infected patients

Vincent Mallet\textsuperscript{a,b,e,*}, Pierre Blanchard\textsuperscript{b,*}, Virginie Verkarre\textsuperscript{a,c}, Anaïs Vallet-Pichard\textsuperscript{a,b,e}, Hélène Fontaine\textsuperscript{b,e}, Caroline Lascoux-Combe\textsuperscript{d} and Stanislas Pol\textsuperscript{a,b,e}

8 out of 97 HIV consecutive patients with unexplained persistent abnormal liver function tests and/or non-cirrhotic portal hypertension

⇒ Histologically confirmed NRH
⇒ Only causes: ddI exposure and HIV
## Noncirrhotic portal hypertension

### Table 1. Literature Review on Noncirrhotic Portal Hypertension (NCPH) in HIV-Infected Persons

<table>
<thead>
<tr>
<th>Author, year of publication</th>
<th>Case definition</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Liver biopsy findings</th>
<th>Proposed risk factors for NCPH or elevated liver enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maida et al, 2006 [5]</td>
<td>Elevated liver enzymes of unknown origin</td>
<td>Case-control (1:1; matched by age, sex, CD4 cell count)</td>
<td>17 with elevated liver enzymes, suspected NCPH in 9 of 17</td>
<td>Biopsy in only 5 of 17: microvesicular steatosis in 5 of 5, mild fibrosis in 3 of 5, cirrhosis in 2 of 5</td>
<td>Prolonged DDI exposure</td>
</tr>
<tr>
<td>Mallet et al, 2007 [6]</td>
<td>Abnormal liver function tests or symptomatic PH of unknown origin</td>
<td>Case series</td>
<td>8</td>
<td>NRH in 7 of 8, sinusoidal dilatation in 1 of 8</td>
<td>DDI exposure (DDI in 8 of 8)</td>
</tr>
<tr>
<td>Sandrine et al, 2007 [8] (letter)</td>
<td></td>
<td>Case report</td>
<td>1</td>
<td>NRH</td>
<td>Exposure to DDI and NVP</td>
</tr>
<tr>
<td>Garvey et al, 2007 [9] (letter)</td>
<td></td>
<td>Case series</td>
<td>6</td>
<td>NRH in 2 of 6, varous outflow obstruction in 3 of 6, normal in 1 of 6</td>
<td>DDI (in 5 of 8), coagulopathy (in 4 of 6)</td>
</tr>
<tr>
<td>Schiano et al, 2007 [10]</td>
<td>NCPH with variceal bleeding; HPS in biopsy; no etiology</td>
<td>Case series</td>
<td>4</td>
<td>HPS in 4 of 4</td>
<td>NVP (current therapy in 3 of 4); ART history not described</td>
</tr>
<tr>
<td>Tateo et al, 2008 [12]</td>
<td>Liver transplantation due to NCPH</td>
<td>Case series</td>
<td>3</td>
<td>NRH in 3 of 3</td>
<td>...</td>
</tr>
</tbody>
</table>

**NOTE.** ART, antiretroviral therapy; DDI, didanosine; HIV, human immunodeficiency virus; HPS, hepatoporal sclerosis; NRH, nodular regenerative hyperplasia; NVP, nevirapine; PH, portal hypertension.
Non-cirrhotic portal hypertension

Unexplained:
- ↓ platelets
- ↑ transaminases
- ↑ alkaline phosphatase, GGT
- E varices, ascites, splenomegaly

Non-cirrhotic portal hypertension

Didanosine consumption

Endothelial dysfunction?
Mitochondrial damage?

High intraportal drug concentration

HIV

Hypercoagulability?

Heterogeneous liver perfusion

Periportal fibrosis

Partial nodular transformation

Nodular regenerative hyperplasia

Non-cirrhotic portal hypertension

Unexplained:
- E varices, ascites, splenomegaly
- E varices, ascites, splenomegaly

Platelet

Transaminases

Alkaline phosphatase, GGT

Endothelial dysfunction?
Mitochondrial damage?
Chronic liver disease in non-alcoholic HIV mono-infected patients

n = 30 HIV mono-infected patients without alcohol abuse and persistent elevated transaminases (>ULN)

1 patient excluded because of nodular regenerative hyperplasia (NRH)

Table 2. Histological Findings in Liver Biopsy of the 30 Patients with Aminotransferase Elevation of Unknown Origin

<table>
<thead>
<tr>
<th>Fibrosis</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>11</td>
<td>36.6</td>
</tr>
<tr>
<td>F1</td>
<td>13</td>
<td>43.3</td>
</tr>
<tr>
<td>F2</td>
<td>2</td>
<td>6.7</td>
</tr>
<tr>
<td>F3</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>F4</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>F1-4</td>
<td>19</td>
<td>63.3</td>
</tr>
</tbody>
</table>

Activity

<table>
<thead>
<tr>
<th>Activity</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0</td>
<td>14</td>
<td>46.7</td>
</tr>
<tr>
<td>A1-3</td>
<td>16</td>
<td>53.3</td>
</tr>
</tbody>
</table>

Steatosis

<table>
<thead>
<tr>
<th>Level</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5%</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>6-30%</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>&gt;30%</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>Macrophagic</td>
<td>12</td>
<td>66.6</td>
</tr>
<tr>
<td>Macrophagic and microphasic</td>
<td>6</td>
<td>33.3</td>
</tr>
</tbody>
</table>

Steatosis and inflammation

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis and inflammation (NASH)</td>
<td>16</td>
<td>53.3</td>
</tr>
<tr>
<td>Steatosis without inflammation</td>
<td>2</td>
<td>6.7</td>
</tr>
<tr>
<td>Inflammation without steatosis</td>
<td>8</td>
<td>26.6</td>
</tr>
<tr>
<td>No steatosis/no inflammation</td>
<td>4</td>
<td>13.3</td>
</tr>
</tbody>
</table>

Fibrosis and activity were classified according to the METAVIR score, and steatosis according to a 3-point scale.
Chronic liver disease in non-alcoholic HIV mono-infected patients

### Table 2. Liver Biopsy Findings (n = 62)

<table>
<thead>
<tr>
<th>Histologic Feature or Diagnosis</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Steatosis</strong></td>
<td></td>
</tr>
<tr>
<td>None to trace (0) (&lt;5%)</td>
<td>17 (27)</td>
</tr>
<tr>
<td>Mild (1) (5%–25%)</td>
<td>26 (40)</td>
</tr>
<tr>
<td>Moderate (2) (25%–60%)</td>
<td>13 (21)</td>
</tr>
<tr>
<td>Severe (3–4) (50%–75%)</td>
<td>7 (11)</td>
</tr>
<tr>
<td><strong>Fibrosis score</strong></td>
<td></td>
</tr>
<tr>
<td>None (0)</td>
<td>43 (69)</td>
</tr>
<tr>
<td>Mild (1)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Moderate (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Bridging (3–4)</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Cirrhosis (5–6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Nonspecific changes</td>
<td>22 (35)</td>
</tr>
<tr>
<td>Steatohepatitis</td>
<td>34 (55)</td>
</tr>
<tr>
<td>Steatohepatitis with any fibrosis</td>
<td>26 (42)</td>
</tr>
<tr>
<td>Steatohepatitis with bridging fibrosis</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Fibrosis (Ishak stage ≥1) without evidence of steatohepatitis</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Bridging fibrosis without steatohepatitis</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Portal venopathy/nodular regenerative hyperplasia</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

All biopsies had at least 10 portal tracts for assessment. Median biopsy length was 15 mm (range, 7–24 mm); 59 of 62 (95%) biopsies were ≥10 mm in length.

* Fibrosis classified according to the Ishak modified histology activity index scoring system [20].

62 HIV mono-infected patients (from USA)

No alcohol abuse

With persistent elevated transaminases and liver histology
NAFLD
Steatosis alone
Steatosis & inflammation
NASH

Potential for progression
Natural history of NAFLD/NASH in non HIV subjects

<table>
<thead>
<tr>
<th>Steatosis</th>
<th>Steatosis/inflammation</th>
<th>Fibrosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
</table>

Steatosis → NASH → Cirrhosis

12-40% → 15%
NASH: reduced survival

- Survival vs. the general population
- Liver-related mortality
- Cardiovascular mortality
- Cirrhosis: an independent risk factor of death
- Hepatocellular carcinoma

STEATOSIS

- Same survival as the general population

METABOLIC SYNDROME (MS) - A Joint definition

**3 criteria out of five**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
</tr>
</thead>
</table>
| Central obesity                              | **Waist circumference:**
|                                              | Europeans: ≥ 94 cm (M) ou ≥ 80 cm (F)                                     |
|                                              | Americans: ≥ 102 (M) ≥ 88 cm (F)                                          |
|                                              | Asians: ≥ 90 cm (M) ≥ 80 cm (F)                                           |
|                                              | Sub-Saharan African: ≥ 94 cm (M) ou ≥ 80 cm (F)                            |
| High Blood Pressure                          | Arterial Pression ≥ 130 mmHg and/or ≥ 85 mmHg or treated Hypertension    |
| Low cholesterol HDL                          | < 0.4 g/L (1 mmol/L) (M) ou < 0.5 g/L (1.3 mmol/L) (F) ou treated Chol   |
| High blood triglycerides                     | ≥ 1.5 g/L (1.7 mmol/L) or treated hyperTG                                 |
| High blood glucose                           | Glucose ≥ 1 g/L (5.6 mmol/L) or antidiabetic treatment                  |

Adapted from Alberti Circulation 2009
The risk of MS is twice in HIV patients

- **MS Prevalence**
  - Controls
  - HIV Patients
  - *P < 0.0001*

- **MS Risk vs Controls**
  - Controls
  - HIV Patients
  - 2.0 (1.6–2.5) *P < 0.0001*
Epidemiology of NAFLD/NASH

France: NAFLD: 60 % NASH: 33 %
De Ledinghen, J Hepatol 2006

Spain: NAFLD: 44%
Caballeria, Eur J Gastro 2012

India: NAFLD 32 %

Japan: NAFLD 29 %
Jimba S Diabet Med 2005

Brazil: NAFLD: 42%
NASH: 27%
27% severe fibrosis/cirrhosis
Cotrim HP, Ann Hepatol 2012

Texas: NAFLD 46 %
12 % NASH
3 % severe fibrosis/cirrhosis
Williams Gastroenterology 2011
Factors associated with the metabolic syndrome in HIV+ subjects

- Overweight and waist circumference
- Lipodystrophy
- Older age
- Insulin resistance
- HAART use of NRTI (D4T, AZT) and/or PIs (indinavir, ritonavir)
<table>
<thead>
<tr>
<th>Study</th>
<th>country</th>
<th>n subjects</th>
<th>Steatosis assessment</th>
<th>Prevalence of NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hadigan, C 2007 JAIDS</td>
<td>USA</td>
<td>33</td>
<td>MR spectroscopy</td>
<td>42%</td>
</tr>
<tr>
<td>Moreno-Torres, A 2007 AVT</td>
<td>Spain</td>
<td>29</td>
<td>MR spectroscopy</td>
<td>58%</td>
</tr>
<tr>
<td>Mohammed, SS 2007 JAIDS</td>
<td>Canada</td>
<td>26</td>
<td>Liver Biopsy</td>
<td>45%</td>
</tr>
<tr>
<td>Guaraldi, G 2008 CID</td>
<td>Italy</td>
<td>225</td>
<td>CT</td>
<td>37%</td>
</tr>
<tr>
<td>Crum-Cianflone, P 2009 JAIDS</td>
<td>USA</td>
<td>216</td>
<td>Ultrasound</td>
<td>31%</td>
</tr>
<tr>
<td>Ingiliz, P 2009 Hepatol</td>
<td>France</td>
<td>30</td>
<td>Liver Biopsy</td>
<td>60%</td>
</tr>
<tr>
<td>Nishijima, T 2014 PlosOne</td>
<td>Japan</td>
<td>435</td>
<td>Ultrasound</td>
<td>31%</td>
</tr>
<tr>
<td>Price, JC 2014 Am J Gastro</td>
<td>USA</td>
<td>465 HIV and HCV</td>
<td>CT</td>
<td>15%</td>
</tr>
<tr>
<td>Juan, M 2014 AIDS</td>
<td>Spain</td>
<td>505 HIV HCV/HBV</td>
<td>CAP™</td>
<td>40%</td>
</tr>
</tbody>
</table>
# NASH and fibrosis in HIV patients

## HIV monoinfected patients with unexplained elevated LFT

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>n subjects</th>
<th>NASH assessment</th>
<th>Prevalence of NASH</th>
<th>Significant fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemoine, M AIDS 2006</td>
<td>France</td>
<td>14</td>
<td>Liver Biopsy</td>
<td>56%</td>
<td>29%</td>
</tr>
<tr>
<td>Mohammed, SS 2007 JAIDS</td>
<td>Canada</td>
<td>26</td>
<td>Liver Biopsy</td>
<td>55%</td>
<td>-</td>
</tr>
<tr>
<td>Crum-Cianflone, N 2009 JAIDS</td>
<td>USA</td>
<td>55</td>
<td>Liver Biopsy</td>
<td>20%</td>
<td>-</td>
</tr>
<tr>
<td>Ingiliz, P Hepatol 2009</td>
<td>France</td>
<td>30</td>
<td>Liver Biopsy</td>
<td>53%</td>
<td>30%</td>
</tr>
<tr>
<td>Sterling, R J Clin Gastr 2013</td>
<td>USA</td>
<td>14</td>
<td>Liver Biopsy</td>
<td>26%</td>
<td>14%</td>
</tr>
<tr>
<td>Morse, CG CID 2015</td>
<td>USA</td>
<td>62</td>
<td>Liver Biopsy</td>
<td>62%</td>
<td>18%</td>
</tr>
<tr>
<td>Vodkin, I APT 2015</td>
<td>USA</td>
<td>33</td>
<td>Liver Biopsy</td>
<td>63%</td>
<td>18.2%</td>
</tr>
</tbody>
</table>
Non-alcoholic steatohepatitis (NASH) in HIV

Physiopathology
Key players

- Mitochondria
- Adipose tissue
- Gut
- Lysosomes
- Endoplasmic reticulum
- Innate immune system
- Genetic
HIV

Oxidative stress
Chronic inflammation state

INSULIN RESISTANCE
Metabolic disorders

Lemoine, M & Ingiliz, P Clin res Hepatol Gastroenterol 2012
Adipose tissue changes
Lipodystrophy and overweight

ART (NRTI, PIs)

Mitochondrial dysfunction
mDNA

Endoplasmic Reticulum Stress

SREBP-1 + lipogenesis

INSULIN RESISTANCE

Free Fatty acids

Autophagy

PPARγ

Leptine, IL6, IL1, TNFα

adiponectine

Genetic

LPS

TNFα

IL-1

NAFLD: the hepatic manifestation of MS

Lemoine, M & Ingiliz P Clin Res Hep Gastr 2012
Intestinal dysbiosis and microbial translocation

- Dysbiosis (imbalance in microbiota)
- Intestinal permeability
- Microbial translocation
- sCD4 and LPS
- Immune activation (TLR)
- Inflammatory cytokines

↑ Systemic inflammation

Liver inflammation & fibrosis

Dinh, DM JID 2015
Miele L et al. 2013
Intestinal dysbiosis and microbial translocation

Stool microbiomal community

HIV neg controls (n=16)
Non obese HIV under HAART (n=21)
Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease

Stefano Romeo1,8, Julia Kozlitina2,3,8, Chao Xing1,2, Alexander Pertsemlidis1, David Cox4, Len A Pennacchio5, Eric Boerwinkle6, Jonathan C Cohen1 & Helen H Hobbs1,7

n = 2,971
Liver Fat content (Spectrometry)
Genomic analysis
In two studies, non-CC variant of rs738049 in the PNPLA3 gene has been shown to be associated with:

- Liver steatosis
- Fibrosis
- Levels of transaminases

Morse, CG et al CID 2015
Price, JC Am J Gastroenterol 2014
Treatment for NASH
Results of the PIVENS trial in non-diabetic NASH

Liver biopsy

PLACEBO
N=83

PIOGLITAZONE (30 mg/d)
N=80

Vitamin E (800 mg/d)
N=84

96 weeks

RESOLUTION OF STEATOHEPATITIS

vitE
P=0.05
P<0.001

PLB
Pio

47

Pioglitazone improved:
• Steatosis
• Inflammation
• Ballooning
• NAS score

IMPROVEMENT PRIMARY ENDPOINT
(in Pts with well defined NASH)

Sanyal, NASH CRN, NEJM 2010
FLINT Phase 2 Trial Design
The Farnesoid X Receptor Ligand Obeticholic Acid (OCA) in NASH Treatment

N=283 Patients w/ Histological Evidence of NASH

Screening (Biopsy)

Placebo QD

Follow up

OCA 25 mg QD

Follow up

72 week Treatment Period

24 week off-drug

Primary endpoint: Histological improvement defined as:
- No worsening in fibrosis; and
- Decrease in NAS of ≥ 2 points

Interim Analysis when 50% of patients completed treatment and had an end-of-treatment liver biopsy

NASH CRN

National Institute of Diabetes and Digestive and Kidney Diseases

Intercept

Tetri, Lancet 2014
Primary Outcome: Improved Liver Histology after 72 Weeks of Treatment

Patients Achieving the Primary Outcome Measure
(2-point or greater improvement in NAFLD activity score without worsening of fibrosis)

- Placebo: 21% (n = 109)
- Obeticholic Acid: 45% (n = 110)

* * *

***p<0.001; Relative risk (95% CI): 1.9 (1.3 to 2.8); p-value and relative benefit were obtained using Cochran-Mantel-Haenszel Chi-square test stratified by center and diabetes status; Missing week 72 biopsy results were imputed as no improvement among patients at risk of week 72 biopsy; Neuschwander-Tetri BA, et al. Lancet. 2014:S0140-6736(14)61933-4.
Secondary Outcomes: Improvement in Histological Parameters

**p<0.05, **p<0.01, ***p<0.001; p-value was based on the Cochran-Mantel-Haenszel chi-square test stratified by center and diabetes status; Neuschwander-Tetri BA, et al. *Lancet.* 2014:S0140-6736(14)61933-4.
Clinical Data with MVC Evaluating Hepatic Fibrosis

Safety and therapeutic efficacy of the switch to maraviroc+darunavir/ritonavir in HIV/HCV coinfected patients: initial results from GUSTA study

NASH study comparing ATV/MVC with NRTI-ART + Vit E histological resolution at 48 weeks
Phase II-study of the CCR2/CCR5 Inhibitors Cenicriviroc (CVC)

**CENTAUR trial**
Global phase 2b study, N = 289

**Key Eligibility Criteria**
- Biopsy diagnosis of NASH with fibrosis
- Enriched for patients with T2DM; high BMI with > 1 criteria of metabolic syndrome; bridging fibrosis and/or definite NASH

**Endpoints**
- **Primary:** Improvement in NAS score without worsening of fibrosis at Year 1
- **Resolution of NASH without worsening of fibrosis at Year 2**

**Others**
- Collagen morphometry
- Fibrosis stage
- α-SMA, CK-18
- Validated fibrosis scores
- Noninvasive imaging
- Biomarkers
- Kidney function

**Primary endpoint biopsy 1 year**

**Final biopsy 2 years**

**1-year-biopsy results end 2016?**

**NCT02217475; EudraCT number 2014-003164-21**
**CVC in steatohepatitis and fibrosis**

- **MCD diet** - progressive steatosis & fibrosis
  
  - 0wks.
  - n=8
  - 4wks.
  - 8wks.

- **Vhc. p.o. 1x/d**
- **CVC p.o. 1x/d**

- **8wks. MCD diet**
- **+4wks. Vhc.**
- **+4wks. CVC**

- **H&E**

- **Steatosis**
  - 0.158

- **Lobular Inflammation**
  - 0.077

- **Hepatocyte Ballooning**
  - ***

- **NAFLD Activity Score**
  - ****

Puengel T, et al., EASL 2016
## Target-Based Drug Classes for NASH

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farnesoid X receptor (FXR) agonist</td>
<td>Obeticholic acid</td>
<td>Breakthrough</td>
</tr>
<tr>
<td>Anti-lysyl oxidase-like 2 monoclonal antibody</td>
<td>Simtuzumab</td>
<td>Fast Track</td>
</tr>
<tr>
<td>Fatty acid/bile acid conjugate</td>
<td>Aramchol</td>
<td>Fast Track</td>
</tr>
<tr>
<td>Dual inhibitor of CCR2 and CCR5</td>
<td>Cenicriviroc</td>
<td>Fast Track</td>
</tr>
<tr>
<td>Dual peroxisome proliferator-activated receptor alpha/delta agonist</td>
<td>GFT505</td>
<td>Fast Track</td>
</tr>
<tr>
<td>Galectin-3-inhibitor</td>
<td>GR-MD-02</td>
<td>Fast Track</td>
</tr>
</tbody>
</table>

*US Food and Drug Administration.
Modest alcohol consumption is associated with decreased prevalence of steatohepatitis in patients with nonalcoholic fatty liver disease (NAFLD)

Winston Dunn, M.D.¹,², Arun J. Sanyal, M.D.³, Elizabeth M. Brunt, M.D.⁴, Aynur Unalp-Arida, M.D., Ph.D.⁵, Michael Donohue, Ph.D.⁶, Arthur J. McCullough, M.D.⁷, and Jeffrey B. Schwimmer, M.D.⁸,⁹ for the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN)¹⁰