Cirrhosis reversibility
Who and Why?

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Fibrosis in Chronic Viral Hepatitis B

- **F0**: lobular organisation, no fibrous tissue
- **F1-F3**: fibrosis (periportal, then bridging)
- **F4**: Cirrhosis = annular fibrosis + architectural remodeling (lobule $\rightarrow$ nodule)

**CIRRHOSIS REVERSION // REGRESSION**

- **F4 $\rightarrow$ F3, F2 or F1**
  - (nodule $\rightarrow$ lobule)
- 1. Degradation of fibrous tissue
- 2. Replacement by hepatocyte (regeneration)
- 3. Restoration of a lobular vascularisation
3-Dimensional organisation of fibrous tissue
Reversion of cirrhosis in animal models

Reversibility of liver cirrhosis

Evidences from clinical trials in viral hepatitis

→ Histologically-proven with repeated biopsies
→ Adequate time interval between repeated biopsies
→ Large sample size (sampling error)
Cirrhosis regression after antiviral treatment

Of the 96 (28%) patients with cirrhosis (Ishak score 5 or 6) at baseline, 71 (74%) no longer had cirrhosis.
Histological outcome in Hep B after long-term tenofovir treatment

- 348 patients with paired biopsies before and after 5 years treatment with tenofovir DF

- 51% (176/348) of patients had fibrosis regression (≥1 unit ↓ in Ishak score) and 96% had prevention of fibrosis progression

- Cirrhosis (Ishak ≥5) regression occurred in 71/96 of patients (74%) with cirrhosis at baseline

Long-term suppression of HBV can lead to regression of fibrosis and cirrhosis

## Main clinical trials in HBV with histological follow-up

<table>
<thead>
<tr>
<th>Reference</th>
<th>Virus</th>
<th>Number of patients enrolled</th>
<th>Therapy</th>
<th>Time to biopsy</th>
<th>Fibrosis regression (%)</th>
<th>Cirrhosis regression % (Regression / cirrhosis at baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dienstag (2003)</td>
<td>HBV</td>
<td>63</td>
<td>LMV</td>
<td>3 yrs</td>
<td>67 %</td>
<td>73 % (8/11)</td>
</tr>
<tr>
<td>Hadziyannis (2006)</td>
<td>HBV</td>
<td>185</td>
<td>ADF</td>
<td>5 yrs</td>
<td>71 %</td>
<td>75 % (7/12)</td>
</tr>
<tr>
<td>Marcellin (2008)</td>
<td>HBV</td>
<td>171</td>
<td>ADF</td>
<td>5 yrs</td>
<td>60%</td>
<td>NA</td>
</tr>
<tr>
<td>Schiff (2011)</td>
<td>HBV</td>
<td>10</td>
<td>ETV</td>
<td>5 yrs</td>
<td>NA</td>
<td>100% (4/4)</td>
</tr>
<tr>
<td>Chang (2010)</td>
<td>HBV</td>
<td>69</td>
<td>ETV</td>
<td>3 yrs</td>
<td>88 %</td>
<td>100% (10/10)</td>
</tr>
<tr>
<td>Marcellin (2013)</td>
<td>HBV</td>
<td>348</td>
<td>TFV</td>
<td>5 yrs</td>
<td>51 %</td>
<td>74 % (71/96)</td>
</tr>
</tbody>
</table>

75-100% of cirrhosis may regress but:

• Small sample size (except TFV study)
• Bias of selection: compensated cirrhosis
• % of cirrhosis regression ↑ % of fibrosis regression??
The influence of sampling error in evaluation of cirrhosis regression

Overestimation of cirrhosis regression because of sampling error
Reversibility of cirrhosis: pending questions

1. Which cirrhosis may reverse?

2. How to assess fibrosis/cirrhosis reversion?

3. What is the risk of HCC after HBV cirrhosis reversion?
CIRRHOSIS: REGRESSION AFTER ANTIVIRAL TREATMENT

Before treatment cirrhosis

6 years after SVR «normal» organisation

1 - Which cirrhosis are reversible?

1. **Thinning of fibrous septa:**
   - Enzymatic degradation of fibrous tissue (metalloproteases, MMP)
   - Collagen cross-links and elastin fibers (old cirrhosis) more resistant to MMP degradation
     → « early » cirrhosis more suitable for degradation

1. **Hepatic regeneration:**
   1. Halting inflammatory reaction
      → Sustained Viral elimination
   2. Internal regenerative potential is variable
      → role of aging? (major telomere shortening)

1. **From nodular to lobular architecture:**
   - Restoration of a trans-lobular blood stream from portal tract to central veins
VASCULAR THROMBOSIS IN CIRRHOSIS

Portal Thrombosis

Central Vein Thrombosis
### WHICH CIRRHOSIS MAY REGRESS?

<table>
<thead>
<tr>
<th>Necessary Mechanisms for regression</th>
<th>Physiopathology Molecular mechanisms</th>
<th>POTENTIAL REVERSION IF:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Thinning of fibrous septa</td>
<td>Enzymatic degradation</td>
<td>EARLY CIRRHOSIS</td>
</tr>
<tr>
<td>2. Hepatocyte regeneration</td>
<td>Halting inflammation</td>
<td>CONTROL OF ETIOLOGY ANTVIRAL DRUGS</td>
</tr>
<tr>
<td>3. Restoration of lobular architecture</td>
<td>Persistent permeable portal and central veins</td>
<td>NO VASCULAR THROMBOSIS</td>
</tr>
<tr>
<td>4. Others</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Altogether, only a limited (?) percentage of cirrhosis may reverse
All Cirrhosis are not alike: a disease with a wide spectrum

The Laennec staging system of cirrhosis

SU Kim, et al. The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis. J Hepatol 2012
Reversibility of cirrhosis: Challenges for the future

1. Which cirrhosis may regress?

2. How to assess cirrhosis reversion?

3. The risk of HCC after cirrhosis regression?
Regression of fibrosis/cirrhosis assessment with non-invasive markers

Longitudinal assessment of liver stiffness by transient elastography for chronic hepatitis B patients treated with NUCs

• Long term NUC treatment for patients with chronic hepatitis B
  - Group A: FibroScan at entry and annually for 3 years (n=22)
  - Group B: FibroScan from 3 to 5 years after the start of NUC treatment

• Results over 3 years after the start of NUC treatment
  - Group A: FibroScan values decreased annually
  - Group B: FibroScan values did not significantly improve

• Rapid decline of liver stiffness in patients with CHB treated with NUC in the first 3 years, followed by a more steady transition from 3 to 5 years

<table>
<thead>
<tr>
<th>Group A (n=22)</th>
<th>FibroScan (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.2 (4.2–28.5)</td>
</tr>
<tr>
<td>FibroScan-1</td>
<td>6.4 (4.0–24.0)</td>
</tr>
<tr>
<td>FibroScan-2</td>
<td>5.8 (3.8–21.2)</td>
</tr>
<tr>
<td>FibroScan-3</td>
<td>5.3 (2.5–18.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group B (n=23)</th>
<th>FibroScan (kPa)</th>
</tr>
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<tbody>
<tr>
<td>Baseline</td>
<td>Not tested</td>
</tr>
<tr>
<td>FibroScan-3</td>
<td>6.1 (3.2–20.5)</td>
</tr>
<tr>
<td>FibroScan-4</td>
<td>6.7 (3.5–23.3)</td>
</tr>
<tr>
<td>FibroScan-5</td>
<td>5.9 (3.0–21.8)</td>
</tr>
</tbody>
</table>

The diagnostic accuracy of TE for diagnosing F4 after treatment was **61% sensitivity**, 95% specificity, and AUROC 0.77.
2 - How to assess cirrhosis reversion after antiviral treatment?

- Non invasive markers validated for progressing fibrosis, not for regressing fibrosis/cirrhosis
  - Role of potential confounding factors other than regressing fibrosis
    - ↓ necroinflammation

- No study with // evaluation of NI markers and histology during regression of cirrhosis
Reversibility of cirrhosis: Challenges for the future

1. Which cirrhosis may reverse?

2. How to assess fibrosis/cirrhosis reversion?

3. What is the residual risk of HCC after HBV cirrhosis regression?
Is it still a risk of liver-related complications after histologically-proven cirrhosis reversion?

Viral suppression/eradication in cirrhotics has beneficial impact on clinical outcome:
- Better survival (van der Meer AJ et al. JAMA. 2012)
- Prevention of hepatic decompensation (Bruno S et al. Hepatology 2010)
- Less need for liver transplantation (van der Meer AJ et al. JAMA. 2012)
- Reduce risk of HCC (Cardoso et al. Journal of Hepatology 2010)

Viral suppression/eradication in cirrhotics has beneficial impact on histology:
- Reduce/reverse fibrosis and cirrhosis

Is cirrhosis reversion a surrogate marker of viral eradication or an independent factor of favourable clinical outcome (↓ HCC risk)
Take-home messages

- Only a subset of compensated cirrhosis may regress histologically even after efficient treatment of viral disease.

- Antiviral therapy is the most efficient anti-fibrotic treatment.

- How to assess cirrhosis reversion is still an open question.

- Reversion of cirrhosis is associated with benefit on clinical outcome.

- Surveillance for HCC should be continued in patients with complete viral suppression even if cirrhosis regression has been achieved.
Thank You!