Advances in Understanding Hepatic Fibrosis and Chronic Liver Disease

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“Fibrosis accounts for \(~45\%\) of all deaths in industrialized nations”

Fibrosis Mechanisms are Similar in Different Organs

Eye
- Strabismus

Skin
- Scleroderma
- Keloid
- Nephrogenic systemic fibrosis

Cardiac fibrosis
- Diastolic dysfunction
- Heart failure, with reduced or preserved ejection fraction
- Arrhythmia

Cirrhosis
- Portal hypertension
- Ascites
- Gastroesophageal varices
- Hepatorenal syndrome
- Hepatopulmonary syndrome
- Portopulmonary syndrome
- Hepatic encephalopathy
- Hepatocellular cancer

Pulmonary fibrosis
- Restrictive lung disease
- Pulmonary hypertension
- Right-sided heart failure

Pancreatic fibrosis
- Chronic pain
- Diabetes mellitus
- Malabsorption
- Cancer

Renal fibrosis
- Chronic kidney disease
- Hypertension
- Anemia
- Electrolyte disturbances

Common Events in Fibrosis Progression and Regression Across Tissues

S. L. Friedman et al., *Sci Transl Med* 2013;5:167sr1-167sr1
Fibrosis is a Common Pathway Among Different Etiologies of Liver Disease

- Inherited Metabolic Disorders
- Excess Vitamin A
- Cholestatic Disorders
- Immune Disorders
- Drugs
- Alcohol
- NASH

Hepatitis Viruses

FIBROSIS
Natural History of Chronic Liver Disease

Chronic hepatitis with fibrosis 10-50 yrs

Normal liver → Cirrhosis

Chronic hepatitis - ~300 million worldwide
HCC - fastest rising tumor incidence

Hepatocellular Carcinoma

Liver Transplant
Hepatic Stellate cells - Perisinusoidal cells of Normal Liver

Hepatic Stellate cell Activation - A Central Event in Liver Fibrosis

Normal Liver

Activated HSC with Fibrosis

Pathways of Stellate cell Activation
Pathogenesis of Hepatic Fibrosis - Updates

Cohen-Naftaly, Therapeutic Adv Gastro, 2012

Illustration by Alessandro Baliani (SAGE Publications Ltd)
NAFLD
Spectrum of Hepatic Pathology

Steatosis

Steatohepatitis

Hepatocellular carcinoma

Cirrhosis
Prevalence of the Metabolic Syndrome in the United States, 2003-2012, NHANES data
Prognostic Implications of NAFLD vs NASH

NAFLD
30% of population
10% of children

NASH + Fibrosis
7-8% of population

Cirrhosis
> 10 years
3%

Cirrhosis
5-10 years
30%

More consistent and rapid progression to cirrhosis
Changing Frequencies of HCV infection and NAFLD as Indications for Liver Transplantation in the U.S.

Data Source: SRTR

Charlton et al. Gastroenterology 141, 1249-1253, 2011
Liver-related mortality

Fibrosis Drives Outcomes in NAFLD
Follow-up of 209 Patients – AFIP, 2010

Rising Contribution of NAFLD to HCC in Newcastle, UK

- NAFLD accounted for 34.8% of HCC
- 30% did not have cirrhosis

Hepatic Fibrosis is Reversible!

- There are no specific anti-fibrotic therapies yet, BUT
- Treatment of the underlying disease is often a very effective antifibrotic (e.g., HBV, HCV)
- These findings indicate that the liver has innate pathways to resorb scar, providing clues to mimicking endogenous pathways with novel therapies
- Recent pre-clinical and clinical data support that cirrhosis is also reversible
Cirrhosis Regression in HCV following Sustained Virologic Response

SVR and All-cause Mortality in Chronic HCV Patients with Advanced Fibrosis

Baseline factors significantly associated with all-cause mortality:
- Older age
- Genotype 3 (2-fold increase in mortality and HCC)
- Higher Ishak fibrosis score
- Diabetes
- Severe alcohol use

<table>
<thead>
<tr>
<th></th>
<th>SVR patients</th>
<th>Non-SVR patients</th>
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<tbody>
<tr>
<td>All-cause mortality</td>
<td>8.9</td>
<td>29.9</td>
</tr>
<tr>
<td>Liver-related mortality or liver transplant</td>
<td>1.9</td>
<td>26.0</td>
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<tr>
<td>HCC</td>
<td>5.1</td>
<td>21.8</td>
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<tr>
<td>Liver failure</td>
<td>2.1</td>
<td>27.4</td>
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</table>

530 patients followed for a median of 8.4 years.

Effect of Bariatric Surgery on NASH

Impact on histology at 1 year after bariatric surgery (82 pts):

Lassailly, Mathurin et al, AASLD Abstract #213, 2014.
Determinants of Reversibility

Duration of injury and fibrosis:
- More rapid onset ➔ more likely regression

Extent and type of cellularity of the scar:
- More cells ➔ more sources of proteases

Cross-linking of the scar:
- More cross-linking (lysyl oxidase, Ttg) ➔ more insoluble

Thickness of the fibrotic bands:
- Thicker septae ➔ more inaccessible to proteases

Balance of proteases (MMPs) and inhibitors (TIMPs):
- High TIMP levels may impede regression

Other factors?
- Genetic determinants of regression?
- Underlying etiology?
Liver Biopsy remains the ‘Gold standard’

- Use Brunt/Kleiner NASH Activity Score (NAS):
  - steatosis
  - ballooning
  - lobular inflammation
  - (fibrosis)

BUT, sampling variability > 40%!
# NAFLD Activity Score (NAS)

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
<th>Extent</th>
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<tbody>
<tr>
<td><strong>Steatosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>&lt;5%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5–33%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>&gt;33–66%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>&gt;66%</td>
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<tr>
<td><strong>Lobular inflammation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>No foci</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>&lt;2 foci/200x</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2–4 foci/200x</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>&gt;4 foci/200x</td>
</tr>
<tr>
<td><strong>Hepatocyte ballooning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Few balloon cells</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Many cells/prominent ballooning</td>
</tr>
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</table>
Measuring Fibrosis – Collagen Proportionate Area (CPA)

Without decompensation

With decompensation

Fibrosis Assessment with Fibroscan®

- Measurements are performed on the right lobe of the liver in intercostal position

- The patient is lying supine with the right arm placed behind his head

Examination time is about 5 minutes

- Interobserver reproducibility
  CVS < 10%
Ripoll et al., *Gastroenterology*, 2007

**HVPG Predicts Clinical Deterioration in Cirrhosis**

*If HVPG < 10 mm, then only ~15% chance of decompensation over 8 yrs*
Quantitative Function Tests in Liver Disease - Correlation with HVPG

- Cholate clearance
- Indocyanine green clearance
- Methacetin breath test
- MEGX
- Galactose elimination
- Methionine breath test
MRI Quantification of Hepatic Fibrosis Using a Novel Collagen-Binding Probe

MR imaging of liver fibrosis with a collagen-targeted probe

Fibrotic: MRI with probe

Control: MRI with probe

\[ \Delta \text{CNR} (\text{Liver}:\text{Muscle}) \]

Liver Hydroxyproline (µg/g)

10
20
30
40

100 150 200 250 300 350

1. Liver biopsy is the standard, but needs to be replaced or complemented by non-invasive markers.

2. Surrogate markers that correlate with clinical outcomes are sorely needed. These may include:
   • Functional tests (incl. HVPG, breath tests, cholate clearance)
   • Novel imaging tests that quantify collagen or fibrolytic enzymes (e.g., lysyl oxidase 2).
   • Tests to measure fat fraction (MR proton density, CAP)

3. Trials in non-cirrhotic patients cannot be powered for clinical outcomes as they will take too long.
How to Shorten the Path to New Anti-fibrotic Drugs?

- **Re-purpose existing drugs:**
  - Angiotensin receptor blockers
  - Tyrosine kinase inhibitors
  - Develop combination drug trials with new + existing agents

- **Identify new biomarkers** that can reveal earlier evidence of activity
  - Serum markers (e.g., LOXL2)
  - MR imaging to quantify hepatic collagen

- **Develop new clinical trial designs**
What are the Features of an Ideal Antifibrotic Trial?

• Optimize selection of a treatment population
  - Use genetic markers to stratify based on risk of progression
  - Establish other markers of progression risk

• Attack molecular targets that are critical to disease pathogenesis
  - Strong validation in human liver
  - Relevant animal models that recapitulate features of human disease

• Establish and apply validated biomarkers that provide early and reliable readouts of drug efficacy
Therapeutic landscape for NASH: one year ago

Actively recruiting Phase 2 trials for treatment of NASH

Clinical trials.gov on April 29, 2013
Therapeutic landscape for NASH: Now

Actively recruiting Phase 2 trials for treatment of NASH

Clinical trials.gov on Oct 22, 2014
Core vs. Regulatory Pathways

**Core:**
- common to ≥2 tissues and species
- earlier evolutionary role
- essential for fibrosis

**Regulatory:**
- affect fibrosis, but more variability between species and tissues
**αv Integrin – A Core Pathway of Fibrosis**

Blockade of αv integrins by a small molecule (CWHM 12) attenuates liver and lung fibrosis.

Therapies for Hepatic Fibrosis in Clinical Trials

1. Reduce primary disease (antivirals)

2. Reduce tissue injury and foster epithelial repair by:
   – Epithelial protectants (FXR ligands, HGF, antioxidants, PPAR α, δ, or γ agonists)
   – Anti-inflammatory agents (esp. chemokine antagonists)
   – Inflammatory cell modulation (macrophage polarization rx.)

3. Block myofibroblast proliferation, contractility & angiogenesis (tyrosine kinase antagonists)

4. Antagonize fibrogenic cytokines and signaling
   (TGFβ1, CTGF antagonism; si-HSP47; hedgehog antagonists)
  Promote apoptosis or reversion of myofibroblasts

6. Stimulate metalloprotease activity by:
   – Antagonize TIMPs (MoAb to TIMP-1)
   – Enhance MMP activity (block collagen cross linking by LOXL2)
FXR ligand (OCA) Reverses Fibrosis in TAA-Induced Liver Disease in Rats

- OCA lowered portal pressure, reduced fibrosis and decreased fibrotic marker expression in rats with TAA induced liver injury compared to control animals.

Source: Friedman et al. AASLD 2005.
FLINT: Primary and Secondary Histological Endpoints

1: Data from Tetri et al. *The Lancet*. Published online November 7, 2014.
2: All p-values compared to placebo.
Effect of Obeticholic Acid on Portal Hypertension

Obeticholic Acid, a Farnesoid X Receptor Agonist, Improves Portal Hypertension by Two Distinct Pathways in Cirrhotic Rats

Len Verbeke,¹ Ricard Farre,²,³ Jonel Trebicka,⁴ Mina Komuta,⁵ Tania Roskams,⁵ Sabine Klein,⁴ Ingrid Vander Elst,¹ Petra Windmolders,¹ Tim Vanuytsel,² Frederik Nevens,¹ and Wim Laleman¹
1. Pathology remains the mainstay for liver disease dx, but will benefit from inclusion of quantitative, well validated measures that correlate with outcomes (e.g., CPA).

2. Current antifibrotic trials still need to include liver biopsy but promising biomarkers and imaging tests could shorten trial duration.

3. Lessons from other organs and novel trial designs can accelerate drug development.

4. We are reaching a ‘tipping point’ of interest and emerging clinical trials that will establish proof-of-principle for antifibrotic drugs.