Anti-fibrotic Therapy in Hepatitis C

*Hot Topics in Liver Disease*
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Hepatic Fibrosis is the Liver’s Wound Healing Response to Many Chronic Injuries

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

**FIBROSIS**
Natural History of Chronic Liver Disease

- **Chronic hepatitis with fibrosis**, 10-50 yrs
- **Cirrhosis**
- **Hepatocellular Carcinoma**
- **Liver Transplant**

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

Challenge # 1: *We need better markers of fibrosis stage and activity*

Challenge # 2: *What makes cirrhosis reversible?*

Challenge # 3: *We need a ‘proof-of-concept’ anti-fibrotic trial!***
Challenge #1:

*We need better markers of fibrosis stage and activity!*

- Too much sampling variability and invasiveness ass’d with liver biopsy
- We need markers that are sensitive, specific and respond quickly to changes in fibrogenic activity
Diagnosis of Hepatic Fibrosis - Current Status

- Lack of robust, standardized endpoints is currently the limiting factor in antifibrotic trials - need is URGENT

- We need BIOMARKERS, not SURROGATES.

- Non-invasive tests (e.g., ELF, Fibrotest) are increasingly specific for early or late stages, but 25-50% indeterminate rate in intermediate stages.
  - Offer an ‘integrated’ readout of fibrosis.
  - May not be sufficient for individual management
  - BUT, they predict outcomes better than biopsy!
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 %

Courtesy of M. Ziol
Transient Elastography for Assessment of Hepatic Fibrosis

- Correlates with “stiffness”
- $R = 0.71$
- ROC = 0.88 for sign fibrosis > F2
- ROC = 0.99 for cirrhosis (F4)

Principles of $^{13}$C Breath Testing

**Concept**

Human Exhalation:
- 78% $\text{N}_2$
- 16% $\text{O}_2$
- 5% $\text{CO}_2$

Constant ratio: $\frac{^{13}\text{CO}_2}{^{12}\text{CO}_2}$
- 1%
- 99%

**Method**

1. **Measure base-line $^{13}$C/$^{12}$C**
2. **Drink $^{13}$C marked substrate**
3. **Substrate targets a metabolic/biochemical process which is affected by presence of the suspected disease**
4. **Rate and magnitude of change in $^{13}$C/$^{12}$C in exhaled breath correlates to presence and severity of the disease**
Readout of Methacetin Breath Test:
Challenge # 2:

What makes Cirrhosis Reversible?

- Not all cirrhosis is the same
- Classification of cirrhosis was never sufficiently refined because it was considered irreversible
- Effective anti-viral therapies have established that even cirrhosis is reversible
Cirrhosis is Reversible!

Evidence in:
- HBV
- HCV
- Secondary biliary cirrhosis
- AIH
- PBC
- Wilson’s disease
- Thalassemia after bone marrow xplant
- Animal models
Improvement in Necroinflammation and Fibrosis from Long-term Entecavir Therapy

Chang, Hepatology, 2010
Reversibility of Cirrhosis Following Treatment of Hepatitis C

Poynard et al, Gastroenterology 2002; 122:1303-1313
Hepatitis C SVR Improves Clinical Outcomes in Cirrhotics, Especially if Cirrhosis Reverses

**Responders vs Non-Responders**

- **P = 0.002**

**Reversers vs Non-Reversers**

- **P = 0.01**

Mallet, V. et. al. Ann Intern Med
2008;149:399-403
Improving Liver Fibrosis has a Functional Impact

SVR of Hepatitis C Lowers HVPG

Roberts et al, Clin Gastro Hep, 2007
Hepatic Stellate cell Activation - A Central Event in Liver Fibrosis

Friedman SL and Arthur, Science and Medicine, 2002
Pathways of Stellate cell Activation

- **Initiation**
  - Injury
    - Oxidative stress
    - Apoptotic bodies
    - LPS
    - Paracrine stimuli
Natural History of Chronic Liver Disease

Chronic hepatitis with fibrosis 10-50 yrs → Cirrhosis

Normal liver → Antifibrotic Therapy → Cirrhosis

Hepatocellular Carcinoma → Liver Transplant
Challenge # 3 - We need anti-fibrotic treatment in a ‘proof-of-concept’ trial!!

- Pharma has a short attention span when drugs fail (e.g., sepsis therapies, stroke prevention)
- Better antiviral therapies for HCV & HBV diminish enthusiasm for anti-fibrotics
- But, many pts still need anti-fibrotics
- A ‘proof of concept’ trial will have an energizing effect on the field
Emerging Therapies for Hepatic Fibrosis

1. Reduce primary disease

2. Downregulate early stellate cell activation

3. Inhibit properties of activated stellate cells: *e.g.*, *proliferation, contractility, fibrogenesis*

4. Stimulate stellate cell apoptosis

5. Degrade “scar” matrix
Reduce Primary Disease:
- Antivirals
- Metabolic therapy

HCV, NASH

Resolution

Friedman SL, J Biol Chem, 2000
Reduce Injury

Resolution

“Hepatoprotectants”

- HGF mimetics
- Antioxidants
- FXR ligands
- PDGF-R antagonists (MoAb, Gleevec)
- RTK antagonists – e.g., Sorafenib
- ET-1 & ET-1 receptor antagonists (Bosentan, Thelin)
- TGFβ1 & TGFβ1 receptor antagonists
- Hepatocyte growth factor agonists
- AT-Receptor antagonists, ACE Inhibitors
  - Adioponectin
  - Cannabinoid R1 antagonists

Resolution

Fibrogenesis
Resolution

HSC Chemotaxis

- PDGF-R antagonists
- Chemokine antagonists
- Chemokine-R antagonists
- Integrin antagonists
Apoptotic ligands, e.g., TRAIL
- TIMP antagonists
- Cannabinoids
Future Advances in Chronic Hepatitis and Hepatic Fibrosis - 2010

• Improved genetic markers of disease risk
• Better non-invasive markers of injury and fibrosis
• Regenerative therapies for acute and chronic liver failure
• Continued refinements in therapies for viral hepatitis - shorter durations, better AE profiles
• Long term antifibrotics, alone or in combination
• Earlier dx and more cures of HCC