Is cirrhosis reversible?

Dr. Jason Chang, MBBS, MRCP(UK), MMed, FAMS
Consultant, Department of Gastroenterology & Hepatology,
Singapore General Hospital
The dogma: Cirrhosis is irreversible

Cirrhosis is associated with *diffuse fibrosis* that involves the entire liver and disrupts its normal architecture; focal areas of fibrosis do not constitute the condition. The fibrosis may consist of delicate interlacing bands or dense broad bands. In general, the scarring is *irreversible* although it is known that collagen turns over continuously and in some form of cirrhosis (e.g., that associated with hemochromatosis) the process may be reversible (p. 554).

Kumar, Cotran, Robbins. Basic Pathology, 5th edition, 1992
Reversibility of cirrhosis: a myth?
Cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of hepatic architecture and formation of regenerative nodules.
Pathogenesis of liver cirrhosis

Chronic liver injury leads to progressive fibrosis which ultimately develops to cirrhosis, leading to portal hypertension, liver failure and HCC.

Fibrosis is a dynamic, bi-directional process which is potentially reversible.
Liver fibrogenesis – the role of hepatic stellate cells
The role of the hepatic stellate cell in fibrogenesis

Friedman, Gastro 2008;134:1655
The role of the extracellular matrix (ECM) in fibrogenesis
Vascular changes in cirrhosis

- Cirrhosis is not just severe fibrosis
- Alterations in the hepatic vasculature are a crucial component of liver cirrhosis
- Establishment of intrahepatic vascular shunts in the fibrous septa bridging the portal tracts and the central vein (portosystemic shunts)
Vascular anatomy in normal liver
Vascular changes in cirrhosis

Zois, Aliment Phar Ther 2008;28:1175
Vascular anatomy in cirrhotic liver

Fig. 1. Liver Biopsy of a patient with hepatitis C infection in the cirrhotic stage, showing a portal-central vascularized septum. Sirius Red stain, original magnification × 100.

Consequence of vascular changes in cirrhosis

- Increased Hepatic Resistance
  - Mechanical: Architectural changes, Fibrosis, Vascular occlusion
  - Dynamic: Endothelial dysfunction, ↑ Vascular tone

- Increased Portal Inflow
  - Splanchnic vasodilation: Increased NO, CO, glucagon, endocannabinoids
  - Hyperkinetic syndrome

- Increased Portal Pressure

\[ \Delta P = \text{Resistance} \times \text{Blood flow} \]
# Reversibility of fibrosis

## Table 1

<table>
<thead>
<tr>
<th>Disease</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>Lamivudine, others</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Interferon alpha(^a)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Bile duct obstruction</td>
<td>Surgical decompression</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Iron depletion</td>
</tr>
<tr>
<td>Alcoholic hepatitis(^b)</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Primary biliary cirrhosis(^b)</td>
<td>Ursodeoxycholic acid, MTX</td>
</tr>
<tr>
<td>Non-alcoholic steatohepatitis(^c)</td>
<td>PPAR gamma ligands</td>
</tr>
</tbody>
</table>

*Abbreviations:* MTX, methotrexate; PPAR, peroxisomal proliferator activated receptor  
\(^a\) or PEG-interferon alpha, with or without ribavirin  
\(^b\) The effect is minimal if present  
\(^c\) Evidence is preliminary at this point  

63 patients with CHB treated with 3y of lamivudine

Biopsies pre-Rx, end of 1 year, end of 3 years

11 (17%) had F4 cirrhosis at baseline

Bridging fibrosis (F3→F2/1) improved in 12/19 (63%)

Cirrhosis improved in 8/11 (73%) – F4→F3 (5), F4→F1 (2), F4→F0 (1)

Dienstag et al, Gastroenterology 2003;124:105-117
Impact of Pegylated Interferon Alfa-2b and Ribavirin on Liver Fibrosis in Patients With Chronic Hepatitis C

THIERRY POYNARD,* JOHN McHUTCION,† MICHAEL MANNS,§ CHRISTIAN TREPO,‖ KAREN LINDSAY,¶ ZACHARY GOODMAN,# MEI–HSIU LING,** and JANICE ALBRECHT** for the PEG-FIBROSIS Project Group

- Pooled data from 4 randomized trials on HCV
- 3010 patients with pre and post treatment biopsy
- Reversal of cirrhosis was seen in 75 (49%) of 153 patients with baseline cirrhosis
- Cirrhosis reversal defined as change in fibrosis score from F4 to F3
- Possibility of sampling error
- Patients with cirrhosis reversal were younger
- All patients excluded decompensated cirrhotics
Long-Term Treatment With Entecavir Induces Reversal of Advanced Fibrosis or Cirrhosis in Patients With Chronic Hepatitis B

EUGENE R. SCHIFF,* SAMUEL S. LEE,*‡ YOU-CHEN CHAO,*§ SEUNG KEW YOON,*‖ FERNANDO BESSONE,*† SHUN-SHENG WU,*# WIESLAW KRYCZKA,** YOAV LURIE,*‡‡ ADRIAN GADANO,*§§ GEORGE KITIS,*‖ SUZANNE BEEBE,*†† DONG XU,*†† HONG TANG,** and UCHENNA ILOEJE*††

A

Knodell necroinflammatory score

<table>
<thead>
<tr>
<th>Score</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–14</td>
<td>2</td>
</tr>
<tr>
<td>7–9</td>
<td>2</td>
</tr>
<tr>
<td>4–6</td>
<td>3</td>
</tr>
<tr>
<td>0–3</td>
<td>3</td>
</tr>
</tbody>
</table>

n = 10

B

Ishak fibrosis score

<table>
<thead>
<tr>
<th>Score</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

n = 10

Figure 1. (A) Distribution of Knodell necroinflammatory scores at 3 biopsy time points taken at baseline, after 48 weeks (year 1) of entecavir therapy, and at the time of long-term biopsy (median, 6 y) among a subset of patients from the long-term histology cohort with an Ishak fibrosis score of 4 or greater at baseline (n = 10). (B) Distribution of Ishak fibrosis scores at 3 biopsy time points taken at baseline, after 48 weeks (year 1) of entecavir therapy, and at the time of long-term biopsy (median, 6 y) among a subset of patients from the long-term histology cohort with an Ishak fibrosis score of 4 or greater at baseline (n = 10).
Resolution of fibrosis

- Role of hepatic macrophages in matrix degradation through increased production of MMP-13
- Clearance of stellate cells by apoptosis
- Cross-linking of collagen by tissue transglutaminase is an important determinant of fibrosis reversibility

Friedman, Gastro 2008;134:1655
All these studies show reversal of fibrosis in cirrhosis BUT

- Reversal in early cirrhosis (diagnosed on histology) but not in clinical cirrhosis, definitely not in decompensated cirrhosis
- No reversal of vascular changes
- Reversal of histological cirrhosis but not clinical cirrhosis

“Point of no return” in cirrhosis
Cirrhosis is a series of progressive stages

Within the spectrum of cirrhosis, the disease is characterized by increases in portal hypertension, matrix cross-linking, thickening of septa and decreased nodule size, portosystemic shunt formation, decreased hepatic function and increased risk of decompensation.

<table>
<thead>
<tr>
<th>METAVIR:</th>
<th>F1-F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVPG:</td>
<td>&gt;5</td>
<td>≥10</td>
</tr>
<tr>
<td>Clinical:</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Stage:</td>
<td>Compensated</td>
<td>Compensated (stage 1)</td>
</tr>
<tr>
<td>Biology:</td>
<td>Fibrogenesis &amp; Neovasc.</td>
<td>Scar x-linking</td>
</tr>
</tbody>
</table>

D’Amico, J Hepatol 2006;44:217
Hepatic venous pressure gradient (HVPG) measurement

- The HVPG is a measure of the portal venous pressure in liver cirrhosis.
- Allows the quantitative measurement of portal hypertension.
- A catheter connected to a pressure transducer is introduced via the internal jugular vein into the hepatic vein via the IVC.
- Direct measurement of free and wedged venous pressures from the hepatic vein.
Fibroscan® - a non-invasive tool for assessment of liver stiffness
Liver Stiffness Measurement Predicts Severe Portal Hypertension in Patients with HCV-Related Cirrhosis

Fig. 1. Linear regression analysis between HVPG and LSM in whole patient population. Abbreviations: HVPG, hepatic vein pressure gradient; kPa, kilopascal.

Vizzutti, Hepatology 2007;45:1290
Controversies in reversibility of cirrhosis

Where is the “point of no return”?  
Speed of reversibility – ideal time to reassess histology to demonstrate reversibility  
Degree of reversibility – partial vs. complete  
Semiquantitative scoring system for fibrosis  
Diagnosis of cirrhosis vs. severity of cirrhosis  
Sampling error of liver biopsy  
Histological reversibility ≠ clinical improvement
Liver cirrhosis is more than just advanced fibrosis – a key feature is architectural distortion and vascular derangements (portosystemic shunting)

Liver fibrosis is reversible (including liver fibrosis in cirrhosis) by treating the underlying cause of liver injury
SUMMARY (2)

- The extent of reversibility of fibrosis is dependent on the degree of cross-linkage of collagen fibres, duration of fibrosis and stability of scar matrix.

- Advanced cirrhosis (with development of portosystemic shunts) is not reversible.
CONCLUSION

Advanced fibrosis / early cirrhosis IS reversible
BUT established cirrhosis is NOT reversible