The Effect of Antiviral Therapy on Liver Fibrosis in CHC
Disclosure

Consultation for Abbvie, BMS, Gilead, MSD, Novartis and Roche pharmaceutical companies.
Outline

• Natural history of hepatitis C infection
• The effect of antiviral therapy on liver fibrosis
• Summary
Liver fibrosis is a common pathway to advanced liver disease

Chronic injury:
- Viral infection
- Alcohol
- NASH
- Autoimmune disorders
- Cholestatic disorders
- Metabolic diseases

Genetic polymorphisms
- Epigenetic marks
- Cofactors (such as obesity and alcohol)

5–50 years

Liver failure
- Portal hypertension

Liver transplant

Normal liver

Inflammatory damage
- Matrix deposition
- Parenchymal cell death
- Angiogenesis

Early fibrosis

Disrupted architecture
- Loss of function
- Aberrant hepatocyte regeneration

Cirrhosis

Resolution

Regression

- Removal of underlying cause
- Anti-fibrotic drug or cell therapy

HCV-induced fibrosis and cirrhosis
HSCs play a key role in pathogenesis of liver fibrosis

Natural History of Hepatitis C

- **Resolved (20%)**
- **Acute hepatitis**
- **Chronic hepatitis (80%)**
  - **Cirrhosis (20%)**
  - **HCC (3-5% / yr)**
Progression of Fibrosis in Chronic Hepatitis C

Rate of Progression of fibrosis in CHC

1382 HALT-C patients screened

Compensated CHC failed to past IFN therapy

545 Patients pre-study with 725 Liver biopsy

344 Liver biopsy >10mm, >4 yr interval

Screen Ishak score cohorts: 2=36, 3=177, 4=67, 5=80, 6=83

Go backwards to include previous biopsies

Analysis GROUP rate of progression slopes

Analysis INDIVIDUAL rate of progression slopes

Gastroenterology 2011;141:900–8
Rapid fibrosis score progression (RFSP) > 0.2 occurred in 26.7% of HALT-C Trial patients

<table>
<thead>
<tr>
<th>Ishak score at screening</th>
<th>Group slope</th>
<th>Years ± screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>.005</td>
<td>-6.4 yr to +4.3 yr</td>
</tr>
<tr>
<td>3</td>
<td>.062</td>
<td>-5.8 yr to +4.3 yr</td>
</tr>
<tr>
<td>4</td>
<td>.090</td>
<td>-5.1 yr to +4.0 yr</td>
</tr>
<tr>
<td>5</td>
<td>.076</td>
<td>-6.8 yr to +4.2 yr</td>
</tr>
<tr>
<td>6</td>
<td>.124</td>
<td>-5.9 yr to +4.3 yr</td>
</tr>
</tbody>
</table>
The RFSP in individuals is 0.35 to 0.97 Ishak units/year

Patients with progression in fibrosis over time

Patients without significant change in fibrosis over time

Gastroenterology 2011;141:900–8
Fibrosis Progression Rate

- 0.12–0.14 units / year
- 1 unit: 7 to 8 years
- Evolution to cirrhosis: 28 – 32 years
Viral and host factors related to HCV spontaneous clearance and disease progress

**Viral factors**
- HCV genotypes
- Quasispecies
- Virus load
- Co-infection

**Host factors**
- Gender
- Age at infection
- Aging process
- Race
- ALT elevation
- Genetic factors (IL-28)
IL-28 and fibrosis progression in CHC: Associated?

The interleukin 28B rs12979860 C/T polymorphism and serum cholesterol as predictors of fibrosis progression in patients with chronic hepatitis C and persistently normal transaminases.


Department of Experimental and Clinical Medical Sciences, Medical Liver Transplantation Unit, Internal Medicine, University of Udine, Udine, Italy.
IL-28 and fibrosis progression in CHC: Associated? YES!

**D**

- rs9380516
  - TT (n=20)
  - CT+CC (n=602)

**B**

- rs4374383
  - AG+GG (n=239)
  - AA (n=57)

*Gastroenterology 2012;143:1244–52*
IL-28 and fibrosis progression in CHC: NOT Associated?

Results from Beijing Friendship Hospital in 2012: rs12979860 and rs8099917 polymorphisms were NOT significantly associated with the FibroScan measurements

Cong R, You H
Outcome of patients infected with the one resource of HCV

One HCV genotype1b donor

Recipients from One Blood Donor (n=105)

Twenty person missed, died or HCV-Ab (-)

Patients with HCV-Ab positive (n=85)

Spontaneous Clearance

HCV RNA Negative (n=27, 31.8%)

Chronic Hepatitis (n=13, 22.4%)

HCV RNA Positive (n=58, 68.2%)

Cirrhosis (n=3, 5.2%)

Without Clearance

Decomp Cirrhosis or HCC (n=0)
Age, not IL-28B, plays important role in both HCV spontaneous clearance and disease progress

**A**

HCV Spontaneous Clearance

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male vs. female)</td>
<td>1.11 (0.59-2.08)</td>
</tr>
<tr>
<td>Age &lt;20 years vs. &gt;20 years</td>
<td>2.04 (1.13-3.69)</td>
</tr>
<tr>
<td>&lt;40 years vs. &gt;40 years</td>
<td>0.81 (0.43-1.54)</td>
</tr>
<tr>
<td>IL-28 rs10853728 CC vs. CG</td>
<td>1.89 (0.91-3.91)</td>
</tr>
<tr>
<td>rs12979860, 8099917, 12980275</td>
<td>2.28 (0.63-8.32)</td>
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**B**

HCV Disease Progress

<table>
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<tr>
<th>Factor</th>
<th>Odds Ratio (95% CI)</th>
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<tr>
<td>Gender (male vs. female)</td>
<td>1.56 (0.41-5.90)</td>
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<tr>
<td>Age &lt;20 years vs. &gt;20 years</td>
<td>0.78 (0.11-5.58)</td>
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<tr>
<td>&lt;40 years vs. &gt;40 years*</td>
<td>0.13 (0.03-0.65)</td>
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<tr>
<td>IL-28 rs 12979860 CC vs. CT</td>
<td>0.87 (0.65-1.18)</td>
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<tr>
<td>rs 8099917 TT vs. TG</td>
<td>0.87 (0.65-1.18)</td>
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</table>
Single source HCV 1b-infected group results support treatment response, not IL-28, as accurate predictor of sustained viral response

SVR=78.7%

IL-28 SNPs ($p=0.355$~0.504)
Response 24W ($p = 0.013^*$)
Fibroscan ($p = 0.033^*$)
A Seven-Gene Signature (Cirrhosis Risk Score) Predicts Liver Fibrosis Progression

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>All 7 SNPs were associated with the risk of cirrhosis with odds ratios 1.86 to 3.23</td>
<td>Cutoff values may only distinguish patients with a very high risk of cirrhosis</td>
</tr>
<tr>
<td>Unique variable associated with fibrosis progression in multivariate analysis, including gender and alcohol intake</td>
<td>Identified in Caucasian patients so it may not be applicable to all ethnic groups</td>
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<td>Mean CRS was significantly higher in untreated in whom fibrosis progressed</td>
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*J Hepatol 2012; 57:1110–25
Hepatology 2009;50: 1038-44*
Outline

- Natural history of hepatitis C infection
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Changes in hepatic inflammation components in the 38 pre- and posttreatment liver biopsies

METAVIR score for fibrosis before and after an SVR

Changes in the areas of fibrosis assessed by morphometry of pre- and posttreatment liver biopsies

Mean change from baseline in METAVIR necroinflammatory (NIF) activity and fibrosis scores (pooled analysis of 1571 patients in 8 trials of phase 2 to 4)

Regression of fibrosis according to treatment response to IFN/PEG-IFN ± RBV

Forty-nine paired pre-treatment and long-term follow-up biopsies in patients with SVR

Pretreatment Ishak scores $\leq 3$

Pre-treatment Ishak fibrosis scores $\geq 4$

Cumulative risk of liver cirrhosis in elderly CHC following treatment

Improvement of platelets after SVR among CHC patients with advanced hepatic fibrosis

Improvement in hepatic inflammation is associated with less fibrosis progression (HALT-C)

Impact of the 10 different regimens on fibrosis stage

Poynard T, Et Al. Gastroenterology 2002;122:1303–13
Evidence for the regression of liver fibrosis in patients treated for CHC

<table>
<thead>
<tr>
<th>Study, [Ref.]</th>
<th>n</th>
<th>Virologic response at study entry</th>
<th>Genotype</th>
<th>Fibrosis stage at index biopsy</th>
<th>Timing of repeat biopsy (mean)</th>
<th>Treatment regime</th>
<th>Length of follow-up (mean)</th>
<th>Histological response on repeat biopsy</th>
<th>Virologic response (end of study)</th>
<th>Clinical response</th>
</tr>
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<tbody>
<tr>
<td>Tsuota (1997), [94]</td>
<td>93</td>
<td>All</td>
<td>GT 1: 42%</td>
<td>93</td>
<td>Mean Scheuer fibrosis score (combined grps A, B and C): 2.3 ± 0.4</td>
<td>15.2 ± 6.7 mo after EOT</td>
<td>Standard IFN-α course</td>
<td>53.6 ± 14.0 mo</td>
<td>Mean Scheuer fibrosis score: 1.5 ± 0.7 (vs. pretreatment score 2.3 (p &lt; 0.001))</td>
<td>No reported virologic relapses during follow-up</td>
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<td>RT study</td>
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<td>Marcelin (1997), [56]</td>
<td>80</td>
<td>All</td>
<td>GT 1: 33%</td>
<td>69</td>
<td>Cirrhosis: n = 6</td>
<td>2.2 ± 1.3 yr after EOT</td>
<td>IFN-α (different regimes according to treatment trial)</td>
<td>4 yr</td>
<td>Improved histology in 94% of patients (decrease ≥ 2 points on Knodell score)</td>
<td>1 patient had definite relapse</td>
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<td>P cohort study</td>
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<td>No patients developed HCC or decompensated liver disease</td>
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<td>Patients included from 6 RCTs of IFN-α</td>
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<td>Reichard (1999), [78]</td>
<td>26</td>
<td>All</td>
<td>GT 1: 41%</td>
<td>23</td>
<td>Scheuer 0-3: n = 22</td>
<td>5 ± 1.8 yr after EOT</td>
<td>IFN-α course (duration of course varied between trials)</td>
<td>5.4 ± 1.8 yr after EOT</td>
<td>Mean fibrosis score post-treatment = 1.0 (vs. pre-treatment score 1.9 (p = 0.008))</td>
<td>2/28 had a late virological relapse &gt;2 yr after EOT</td>
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<tr>
<td>P cohort study</td>
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<td>HCC/liver-related deaths not specifically reported</td>
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<td>George (2008), [29]</td>
<td>150</td>
<td>All</td>
<td>GT 1: 53%</td>
<td>60</td>
<td>Scheuer stage 1: n = 27</td>
<td>4 yr after EOT</td>
<td>IFN-α+RBV: n = 146</td>
<td>5 yr</td>
<td>39/49 (80%) had a decrease in fibrosis stage</td>
<td>No patients with definite relapse</td>
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<tr>
<td>P cohort study</td>
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<td>(49%)</td>
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<td>Deaths: n = 1 (recurrent liver cancer post OLT)</td>
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<td>Total: n = 146</td>
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<tr>
<td>Toccatelli (2008) [93]</td>
<td>112</td>
<td>Sustained responder*</td>
<td>n = 87</td>
<td>112</td>
<td>Mean Knodell fibrosis score: Sustained responder Grp (n = 87): 1.2 ± 1.1</td>
<td>2.5 ± 1.2 yr after EOT (range 12-76 mo in sustained responder grp)</td>
<td>Standard IFN-α course</td>
<td>3 yr minimum</td>
<td>29/66 (44%) of sustained responder grp with abnormal index fibrosis score had decreased fibrosis score post-treatment, 37 (56%) had an unchanged score. None had increased score 3/21 relapsers with abnormal index fibrosis score had decreased score after treatment, 15 had unchanged fibrosis and 3 had increased score (p &lt; 0.001 vs. SVR grp)</td>
<td>No late virologic relapses in sustained responder grp</td>
</tr>
<tr>
<td>RT multi-centre study</td>
<td></td>
<td>Sustained responder</td>
<td>Relapsers: n = 25</td>
<td></td>
<td>1.6 ± 1.2</td>
<td>2 ± 0.7 yr after EOT (range 12-31.4 mo in relapers)</td>
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</tbody>
</table>

Liver-related event and death in patients ± SVR (Left) and in patients ± regression of cirrhosis (Right) after IFN-based therapy

Survivals in CHC Patients With Advanced Fibrosis ± SVR

van der Meer AJ, et al. JAMA 2012
Could DAA therapies improve liver fibrosis in CHC?

- So far no DAA clinical trials use liver histology as endpoint
  - The efficacy is too high
  - The duration of treatment is too short
  - Long-term follow-up studies on the histological or clinical outcomes (including development of cirrhosis, decompensation, HCC or survival) are warranted
Outline

- Natural history of hepatitis C infection
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Summary

- HCV infection carries a high risk of progression of liver fibrosis
- SVR induced by IFN-based therapy could attenuate the progression or accelerate the regression of liver fibrosis
- Regression of liver fibrosis reduces the liver events and improves survival
- DAA therapy should also achieve the same but needs to be verified by long-term follow-up studies