EVALUATION OF FIBROSIS AND STEATOSIS WITH NON INVASIVE METHODS

Comments from pathologist

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• To emphasize some important questions raised from pathology when discussing non invasive evaluation of:
  
  – FIBROSIS

  – STEATOSIS
Fibrosis: The major histological prognostic factor

Survival to liver-related complications according to liver fibrosis stage on initial biopsy in Hepatitis C

Histological stage of fibrosis predicts survival in NASH
Normal liver, Masson’s trichrome
Comment 1: NOT ALL FIBROSIS ARE ALIKE

NORMAL LIVER LOBULE

PERIPORTAL SPREADING FIBROSIS

PERICENTRAL SPREADING FIBROSIS

CHRONIC VIRAL HEPATITIS

NAFLD
FIBROSIS IN CHRONIC HEPATITIS

F0

F2
  PT
  CV

F3

F4
SPECIFICITY OF FIBROSIS IN NAFLD

PERICENTRAL FIBROSIS

PERISINUSOIDAL FIBROSIS
Comment 2: AMOUNT OF FIBROSIS DIFFERENT FROM STAGE OF FIBROSIS

Amount of fibrosis (morphometry) and histological stage

![Graph showing the relationship between Ishak stage category and area of fibrosis (in %)]

<table>
<thead>
<tr>
<th>Histological</th>
<th>F1-F3</th>
<th>F4 (Cirrhosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Non-cirrhotic</td>
<td>Compensated</td>
</tr>
<tr>
<td>Symptoms</td>
<td>None</td>
<td>None (no varices)</td>
</tr>
<tr>
<td>Sub-stage</td>
<td>-</td>
<td>None (varices present)</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td>&gt;6</td>
<td>&gt;10</td>
</tr>
<tr>
<td>(INR/GGT)</td>
<td>&gt;12</td>
<td>&gt;12</td>
</tr>
</tbody>
</table>

- **Non-cirrhotic**
  - None
- **Compensated**
  - None (no varices)
  - Stage 1
- ** Decompensated**
  - Ascites, VH, Encephalopathy
  - Stages 3 and 4

Garcia-Tsao G, et al. Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis. Hepatology 2010; 51: 1445–9

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
LAENNEC SCORING SYSTEM OF CIRRHOSIS

4a

- Thin fibrous septa
- Regenerative nodules

4b

4c

- Thick fibrous septa
- Atrophic nodules

The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis SU Kim, HJ Oh, IR. Wanless, S Lee, YN Park, J Hepatol 2012

Clinical relevance of scoring cirrhosis

The Laennec staging system for histological sub-classification of cirrhosis is useful for stratification of prognosis in patients with liver cirrhosis. 

Kim, HJ Oh, IR. Wanless, S Lee, YN Park, J Hepatol 2012
Comment 4: Cirrhosis may regression after antiviral treatment.

Impact of Pegylated Interferon Alfa-2b and Ribavirin on Liver Fibrosis in Patients With Chronic Hepatitis C

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See editorial on page 1525.

Background & Aim: Liver fibrosis is an important prognostic factor in patients with hepatitis C. The effect of pegylated (PEG) interferon alone or in combination with ribavirin on fibrosis has not been established. Methods: We pooled individual data from 2010 naive patients with pretreatment and posttreatment biopsies from 4 randomized trials. Ten different regimens combining standard interferon, PEG interferon, and ribavirin were compared. The impact of each regimen was estimated by the percentage of patients with at least 1 grade improvement in the necrosis and inflammation (METAIVR score), the percentage of patients with at least a stage worsening in fibrosis (METAIVR score), and by the fibrosis progression rate per year. Results: Necrosis and inflammation improvement ranged from 20% (interferon 24 weeks) to 72% (optimized PEG 1.5 and ribavirin, P < 0.001). Fibrosis worsening rates from 23% (interferon 24 weeks) to 8% (optimized PEG 1.5 and ribavirin, P < 0.001). All regimens significantly reduced the fibrosis progression rates in comparison to rates before treatment. The reversal of cirrhosis was observed in 75 patients (49%) of 153 patients with baseline cirrhosis. Six factors were independently associated with the absence of significant fibrosis after treatment: baseline fibrosis stage (odds ratio [OR] = 0.12, P < 0.0001), sustained viral response (SVR) (OR = 0.36, P < 0.05), cirrhosis with diabetes (OR = 0.48, P = 0.004), age at diagnosis (OR = 0.98, P = 0.003), and baseline platelet count (OR = 0.31, P = 0.002). Of the 96 (28%) patients with cirrhosis (Ishak score 5 or 6) at baseline, 71 (74%) no longer had cirrhosis. The reversal of cirrhosis was observed in 75 patients (49%) of 153 patients with baseline cirrhosis.

Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study

Patrick Maurice, Edward Curry, Maria Bac, Necmen Aydin, William Seller, Ian J Jacobson, Amy Kay Washington, George Gornitsky, John B Fatheree, Brad Auger Schd, Jeffrey D Bumstead, Kathelyn A Kicins, Gaurav Subramanium, John G Mckibbin, Jimly Kitchfoot

Summary

Background: Whether long-term suppression of replication of hepatitis B virus (HBV) has any beneficial effect on regression of advanced liver fibrosis associated with chronic HBV infection remains unclear. We aimed to assess the effects on fibrosis and cirrhosis of at least 5 years’ treatment with tenofovir disoproxil fumarate (DF) in chronic HBV infection.

Methods: After 48 weeks of randomised double-blind comparison (Japanese NCT00176767 and NCT00181809) of tenofovir DF with active comparator, participants (positive or negative for HBeAg) were eligible to enter a 5-year study of open-label tenofovir DF treatment, with a pre-specified repeat liver biopsy at week 240. We assessed histological improvement (≥2-point reduction in Knodell necroinflammatory score with no worsening of fibrosis) and regression of fibrosis (≥1 unit decrease in Ishak scoring system).

Findings: Of 641 patients who received randomised treatment, 585 (91%) entered the open-label phase, and 493 (84%) completed 240 weeks. 316 patients (51%) had biopsy results at both baseline and week 240. 304 (87%) of the 348 had histological improvement, and 176 (51%) had regression of fibrosis at week 240 (p > 0.0001). Of the 96 (28%) patients with cirrhosis (Ishak score 5 or 6 at baseline, 71 (74%) no longer had cirrhosis (≥1 unit decrease in score), whereas 35 of 252 patients without cirrhosis at baseline progressed to cirrhosis at year 5 (p = 0.0003). DF was safe and well tolerated at 5 years of therapy. 137 (21%) patients with fibrosis had adverse events, but only nine patients had serious events related to the study drug.

Interpretation: In patients with chronic HBV infection, up to 5 years of treatment with effective, long-term suppression of HBV can lead to regression of fibrosis and cirrhosis.
Histological outcome of Hepatitis B during long-term Tenofovir treatment

- 5 year treatment with tenofovir DF in HBeAg-ve and +ve patients
- 348 patients with paired biopsies before treatment, at Year 1 and Year 5
- 96% of patients with paired biopsies either improved fibrosis score or did not change at year 5
- Cirrhosis regression (Ishak score ≥5) occurred in 74% of patients with cirrhosis at baseline

1. Marcellin P, et al. AASLD 2011; Poster #1375
61% patients with F4 at baseline had cirrhosis regression to lower METAVIR stages

- 38 patients, Cirrhosis C, Child-Pugh A - 24/48 weeks standard bitherapy and SVR
- Paired biopsy, mean interval: 6 years, mean length 25mm
The relationship of regression of cirrhosis to clinical outcome in Hep C

- 96 patients with biopsy-proven Hep C cirrhosis treated with an Ifn-based regimen and post-treatment liver biopsy (median follow-up: 118 months)

- 18 patients had regression of cirrhosis.

- The incidence of LRE was 0 per 100 patient/years in patients with regression of cirrhosis and 4 in patients without regression of cirrhosis

- The transplantation-free survival rate at 10 years was 100% in patients with regression of cirrhosis and 74.2% in patients without regression of cirrhosis

Regression of cirrhosis is associated with decreased Liver-related morbidity and improved survival

Liver-related events were hepatocellular carcinoma, hepatic encephalopathy, variceal bleeding, ascites, spontaneous bacterial peritonitis, and liver transplantation.


Number of liver biopsy per year from 2000 to 2013 for chronic viral hepatitis in Beaujon hospital
FIBROSIS : questions from the pathologist?

• Different type of fibrosis: one single or several different tools?
• Can we assess the different stages of cirrhosis uninvasively?
• Fibrosis regression: how to evaluate it non invasively?
• Given the low accuracy of NI tools to differentiate between intermediate stages of fibrosis (F1 vs F2 or F2 vs F3), is it realistic to rely on staging fibrosis with these NI tools in antiviral treatment guidelines.
Hepatic metabolism of Free Fatty Acid

• Steatosis (0-3)  0 = <5%, 1 = 5-33%, 2 = 34-66%, 3 = >66%
NAFLD: a spectrum of histological patterns

NAFLD: non-alcoholic fatty liver disease

- STEATOSIS (NAFL)
- STEATOHEPATITIS (NASH)
- FIBROSIS
- CIRRHOSIS
- HCC
Non Alcoholic Steatohepatitis (NASH)

> 5% steatosis (≥ grade 1)
+ Lobular inflammation of any degree (≥ grade 1)
+ Liver cell ballooning of any amount (≥ grade 1)

“Endpoints and Clinical Trial Design for Nonalcoholic Steatohepatitis.”
HEPATOLOGY 2011;54:344-353
• Activity (0-4) : Ballooning (0-2) + Lobular inflammation (0-2)
NASH: A histological disease clinically relevant

Overall survival in patients with steatosis and NASH

Cumulative LRM according to presence of NASH in index liver biopsy

Liver Related Mortality

Patients with NASH have higher risk of liver mortality than steatosis

Matteoni CA, Younossi, Z, Gralich T et al. Gastro, 1999

• Fibrosis (0 – 4) 1a,b,c = perisinusoidal or periportal fibrosis, 2 = both perisinusoidal and periportal fibrosis, 3 = bridging fibrosis, 4 = cirrhosis
NASH (NAS > 5) have no deleterious evolution compared to a control population if fibrosis <3

S.A.F.

S2A4(2+2)F4
STEATOSIS : questions from the pathologist ?

• Accuracy of NI tools to evaluate amount of steatosis ?

• Do NI tools differentiate steatosis from NASH ?

• How to detect non invasively both NASH and fibrosis : does steatosis/NASH influence fibrosis accuracy detection with NI methods in NAFLD ?