Is it still a place for liver biopsy in chronic viral hepatitis (C and B)?

The opinion of a pathologist

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Number of liver biopsy per year from 2000 to 2013 for chronic viral hepatitis in Beaujon hospital
Issues to be discussed

• Is there remaining indications of liver biopsy in hepatitis C?

• Liver biopsy in hepatitis B

• Liver biopsy in the context of fibrosis regression after antiviral treatment
Is there remaining indications of liver biopsy in hepatitis C?

Decline in the indications of liver biopsy in Hep C

- Major progress of antiviral treatment in Hep C:
  - Highly efficient
  - Wide indications
  - Short duration
  - Adverse events well-characterized

- Liver biopsy is no more useful:

  clinical issues: cirrhosis vs non-cirrhosis?, normal liver vs any fibrosis?

  → non invasive markers (serum, Fibroscan)
Is there remaining indications of liver biopsy in hepatitis C?

When to perform still a liver biopsy in hepatitis C:

- Evidence of comorbidities
NAFLD and HEP C

Hep C and simple steatosis
Hep C + NASH: portal fibrosis (HepC) + central fibrosis (NASH)
When to perform still a liver biopsy in hepatitis C:

- Evidence of comorbidities
  - Others: drug interaction, iron, granulomas...... and unexpected associated diseases
- Discordances between non invasive markers (serum vs Fibroscan) or non invasive markers and symptoms
- Patients difficult to treat, retreatment, any complex situation
- Follow-up of transplanted patients for cirrhosis C

Remaining indication of liver biopsy in Hep C: 10 – 20% of Hep C patients in tertiary care hospital
Is there remaining indications of liver biopsy in hepatitis C?

Comments?

Questions?
Number of liver biopsy per year from 2000 to 2013 for chronic viral hepatitis in Beaujon hospital

- Green line: Hépatite C
- Red line: Hépatite B
Liver biopsy in hepatitis B

• Different context than Hep C:
  ○ Viral Suppression not eradication
  ○ Long-term treatment
  ○ Cost, observance
  ○ Adverse events after long-time use?

→ Helpful to decide the best timing for starting treatment: not too early – not too late (in addition to viral makers and transaminases)
Hepatitis B: natural history is more complex

Neither HBV DNA quantification, HBs Ag, transaminases or HBeAg allow, alone or in combination, to assess histological severity (grade and stage)
Liver biopsy should be considered in pre-treatment evaluation of HEP B (EASL guidelines 2012)
Liver biopsy in Hepatitis B

**CON:**
- Invasive
- Acceptability
- Accessibility
- Cost
- Sampling error

**PRO:**
- Gold Standard
- Fibrosis ....but not only
- NI markers risk of errors:
  - LB is the reference for serum marker : LB error impact accuracy of NI markers
  - Histological confounding patterns
From Paris (F0) to Marseille (F4)

Non invasive markers

Liver biopsy
From Paris (F0) to Marseille (F4)

- Non invasive markers: static evaluation of fibrosis
- Liver biopsy: dynamic evaluation of fibrosis
Liver biopsy: fibrosis but not only..... Fibrosis in its microenvironment

Septal fibrosis (F3), no necroinflammation
Liver biopsy: fibrosis in its microenvironment

Septal fibrosis (F3), severe activity
Hepatitis B, necroinflammation and fibrosis evaluation

- Inflammation: a characteristic histological pattern in Hepatitis B

- Necroinflammation: confounding factor in fibrosis evaluation with non-invasive marker (serum markers and Fibroscan) in the context of Hep B
Viral reactivation: Fibroscan = 25 Kpa, Fibrosis F2
Liver biopsy has still a significant role in hepatitis B

Comments?

Questions?
Issues to discuss

• Is there remaining indications of liver biopsy in hepatitis C?

• Liver biopsy in Hepatitis B

✓Liver biopsy in the context of fibrosis regression after antiviral treatment (Hep B, Hep C)
Fibrosis: complex, resistant and stable architecture

- Fibrous septa
- Fibres
- Fibrills
- Collagen molecules (Lox)
Cirrhosis of the liver: a reversible disease?
Perez-Tamayo R. Pathol Annu 1979;14:183-213

Ccl4

W1  W2  W3  W4  W5  W6
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 & Aims: Liver fibrosis is an important prognostic factor in patients with hepatitis C. The effect of pegylated (PEG) interferon alone or its combination with ribavirin on fibrosis has not been established. Methods: We pooled individual data from 3010 naïve patients with pre-treatment 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 (METAIVIR score), the percentage of patients with at least 1 stage worsening in fibrosis (METAIVIR score), and by the fibrosis progression rate per year. Results: Necrosis and inflammation improvement ranged from 39% (interferon 24 weeks) to 73% (optimized PEG 1.5 and ribavirin; P < 0.001). Fibrosis worsening ranged 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 comparision 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 presence of significant fibrosis after treatment: baseline fibrosis stage (odds ratio [OR] = 0.12; P < 0.0001), sustained viral response (OR = 0.36; P < 0.0001), age < 40 years (OR = 0.51; P < 0.001), body mass index < 27 kg/m² (OR = 0.65; P < 0.001), no or minimal baseline activity (OR = 0.70; P = 0.02), and viral load < 3.5 millions copies per milliliter (OR = 0.79; P = 0.03). Conclusions: PEG-interferon and ribavirin combination significantly reduces the rate of fibrosis progression in patients with hepatitis C.

Aproximately 170 million people worldwide are infected with chronic hepatitis C virus (HCV). The degree of histologic fibrosis is an important marker of the stage of the disease because the natural history of hepatic cirrhosis involves the gradual progression of hepatic fibrosis that can eventually lead to cirrhosis. Most of the complications related to chronic infection occurs in patients who have established cirrhosis. Treatment that could halt or diminish the progression of fibrosis would theoretically be beneficial. We have previously reported that the combination regimen of interferon and ribavirin shows progression of liver fibrosis and even leads to regression in a proportion of patients. The impact on fibrosis was related both to the response to therapy and the duration of interferon treatment. Recently, it has been shown that the pegylated form of interferon (PEG-interferon) has a significantly higher efficacy in achieving sustained response in comparison to standard interferon. This greater efficacy has been observed both for monotherapy*•† or in combination with ribavirin. The effect of these new regimens on historical cirrhosis was observed in 75 patients (49%) of 153 patients with baseline cirrhosis.

The reversal of cirrhosis was observed in 75 patients (49%) of 153 patients with baseline cirrhosis.

Materials and Methods

The individual data from 4 randomized trials of PEG-interferon alpha-2b alone (Peginteron, Schering Plough, Kenilworth, NJ), or in combination with ribavirin, or of the combination

Abbreviations used in this paper: PEG, pegylated; TNF, three times per week.

© 2002 by the American Gastroenterological Association 0016-5085/02/2836-00 do:10.1053/gast.2002.33623
Evolution histologique de la fibrose dans l’hépatite B après suppression virale

- **Lamivudine**: 63 patients, regression de la fibrose septale chez 12/19 (63%) et de la cirrhose chez 8/11 patients (73%)
  

- **Adefovir**: Régression de F3 / F4 chez 7/12 patients (58%)
  

- **Entecavir**: 88% des patients réduisait leur score de fibrose dont tous les patients avec fibrose septale ou cirrhose au départ
  
Histological outcome in Hep B after long-term tenofovir treatment

- 348 patients with paired biopsies before and after 5 years treatment with tenofovir DF

- 51% (176/348) of patients had fibrosis regression (≥1 unit ↓ in Ishak score) and 96% had prevention of fibrosis progression

- Cirrhosis (Ishak ≥5) regression occurred in 71/96 of patients (74%) with cirrhosis at baseline

Long-term suppression of HBV can lead to regression of fibrosis and cirrhosis

61% patients with F4 at baseline had cirrhosis regression to lower METAVIR stages
CIRRHOSIS C
PRETREATMENT BIOPSY

1 year AFTER SVR

6 years AFTER SVR
Evolution of fibrosis in chronic viral hepatitis

Natural History → Treatment →
Regression of fibrosis / cirrhosis
Questions pending

• Is histological regression of cirrhosis clinically relevant?

• Which cirrhosis may regress after viral eradication/suppression?

• How to evaluate fibrosis regression?
Clinical relevance of histological regression

The relationship of regression of cirrhosis to 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 annual incidence of LRE was 0% 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

clinical relevance to assess fibrosis/cirrhosis regression
Which cirrhosis may regress?
Pathophysiology of cirrhosis regression

Liver Biopsy, 6 years after SVR
Which cirrhosis may regress?

1. Thinning of fibrous septa: Enzymatic degradation of fibrous septa:
   - **Early cirrhosis**

2. Reshaping of portal tract: Persisting portal vessels and central veins within annular fibrous tissue
   - **Absence of extensive vascular thrombosis**

3. Hepatocyte regeneration: arrest of necroinflammation
   - **To treat the etiology of the disease**
Laennec score of cirrhosis

4a
- Thin fibrous septa
- Regenerative nodules

4b
- Thick fibrous septa
- Atrophic nodules

4c

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

How to assess cirrhosis/fibrosis regression?

Liver biopsy?

Non invasive markers?
How to assess cirrhosis/fibrosis regression?

Liver biopsy

- Histological staging system defined for stable or progressing fibrosis, not for regressing cirrhosis
- Specific histological features of regressing fibrosis not included in scoring systems
- Sampling error in regressing fibrosis unknown
Mr B... F, cirrhose C

Avant Ttmt : F4

6 ans après traitement et SVR: F4

Score Laennec : F4 b → F4a
Collagen Proportional area (morphometry)
Comparison before and after SVR

How to assess cirrhosis/fibrosis regression?

Non invasive markers

- Serum markers: defined with liver biopsy with stable or progressing fibrosis, not with regressing fibrosis
- Fibroscan, serum markers: role of confounding histological features (regression of necroinflammation)
How to assess regression of liver fibrosis/cirrhosis after antiviral treatment

Answer: ??

Comments?

Questions?