Update on Non-Alcoholic Fatty Liver Disease

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Disclosure

- Clinical trials: Genfit
- Speaker’s Bureau: none
- Advisory Board: none
Non-alcoholic Fatty Liver Disease (NAFLD)

Non-alcoholic Fatty Liver (NAFL)

Steatosis (fat in hepatocytes)

Non-alcoholic Steatohepatitis (NASH)

Steatosis
Cell injury
Ballooning
Mallory Bodies
Inflammation
Fibrosis

Cryptogenic Cirrhosis

NASH Cirrhosis
Non-Alcoholic Fatty Liver
(“Simple” Steatosis)
Steatohepatitis (NASH): Hepatocyte Injury

Ballooning (swelling)  Mallory Bodies (inclusions)
Steatohepatitis (NASH)

Inflammation

Pericellular Fibrosis
# NAFLD Activity Score (NAS) and Fibrosis

## NAFLD Activity Score (NAS)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Points</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatosis</td>
<td>0</td>
<td>&lt;5%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5-33%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>&gt;33 to 66%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>&gt;66%</td>
</tr>
<tr>
<td>Lobular Inflammation</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>&lt;2 foci per 200x field</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2-4 foci per 200x field</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>&gt;4 foci per 200x field</td>
</tr>
<tr>
<td>Ballooning</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Few ballooning cells</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Many/prominent ballooning</td>
</tr>
</tbody>
</table>

## NAS Score
0-2 Likely not NASH  
3-4 Indeterminate  
5-8 Likely NASH

## Fibrosis stage

<table>
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<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>I Zone 3 pericellular, focal or extensive</td>
</tr>
<tr>
<td>II Zone 3 pericellular, With periportal fibrosis</td>
</tr>
<tr>
<td>III Zone 3 pericellular, With portal bridging</td>
</tr>
<tr>
<td>IV Cirrhosis</td>
</tr>
</tbody>
</table>

Kleiner et al. Hepatology 2005;41:1313
NAFLD Prevalence in US:  
*Ethnicity*

- NAFLD-Overall: 46%
- NAFLD-Hispanic: 58.3%
- NAFLD-Caucasian: 44.4%
- NAFLD-African American: 35.1%
- NASH-Overall: 12.2%
- NASH-Among Diagnosed NAFLD: 29.9%

Source: Williams, Gastro 2011
Natural History of NAFLD

- **Isolated Fatty Liver**
  - None to very minimal progression to fibrosis
  - No ↑ risk of death compared with the general population

- **Fatty Liver with Mild Inflammation**
  - Possible sampling variability with some risk of progression

- **NASH**
  - ↑ risk of death compared with general population
    - Cardiovascular, malignancy, liver-related
  - NASH with fibrosis portends worse prognosis
    - Fibrosis progression associated with diabetes, severe IR, weight gain >5 kg, rising ALT, AST
  - ~11% over 15 years, but significant variability

- **NASH Cirrhosis**
  - ~7% over 6.5 years

- **HCC**
  - ~31% over 8 years

- **Decompensation**

NAFLD Diagnosis

• Requires:
  – Hepatic steatosis on imaging or histology
  – Exclusion of other causes of hepatic steatosis / liver injury

• Lack of significant alcohol use
  – <21 drinks/week for men, <14 drinks/week for women

• Typically associated with metabolic risk factors:
  – DM
  – Obesity
  – Hyperlipidemia/triglyceridemia

• **NASH diagnosis requires Liver Biopsy**

Joint AGA, AASLD, ACG Guidelines on NAFLD 2012
Prevalence of NAFLD in patients with features of the metabolic syndrome

- Normal: 23%
- Hypertension: 30%
- Hyperlipidemia: 50%
- Metabolic syndrome: 70%
- Diabetes: 70%
- Obesity: 90%
Predictive Value of Aminotransferases in NAFLD

Serum ALT can be normal in up to nearly 60% of NAFLD patients with NASH\textsuperscript{1}

Serum ALT can be increased in up to 53% of NAFLD patients with no NASH\textsuperscript{2,3}

Therefore, serum ALT level alone is not predictive of NASH or fibrosis level\textsuperscript{1-3}

- Normal ALT cannot rule out progression or NASH
- Increased ALT cannot predict NASH

Abbreviations: ALT, alanine aminotransferase; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
Noninvasive Tests for Liver Fibrosis & Fat

• Clinical or laboratory tests
  – NAFLD Fibrosis Score (www.nafldscore.com)
  – FIB-4 index
  – Enhanced Liver Fibrosis (ELF) (not in US)

• Imaging modalities
  – Shear-wave elastography
    • Fibroscan, supersonic imaging, ARFI
  – MRI-based
    • Magnetic Resonance Elastrography (MRE)
    • Liver MultiScan

• Fat in liver
  – Controlled Attenuation Paramater (Fibroscan-based)
  – MRI – Proton Derived Fat Fraction (PDFF)

Abbreviations: ALT, alanine aminotransferase; ARFI, acoustic radiation force impulse; AST, aspartate aminotransferase; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease.
Transient Elastography

- FibroScan® is based on patented technology: Vibration Controlled Transient Elastography (VCTE™)

- Allows painless and simultaneous measurement of two quantitative parameters:
  - Liver stiffness expressed in kPa
    → Correlated to liver fibrosis [1]
  - Controlled Attenuation Parameter (CAP™) expressed in dB/meter
    → Correlated to liver steatosis [2]

- Both quantitative parameters are assessed on the same volume of liver tissue (3cm³)
  - 100 times bigger than liver biopsy

[FibroScan® 502 TOUCH]
MR Elastography in NAFLD

AUROC for diagnosis of advanced fibrosis

For Stage 3-4 fibrosis: >3.63 kPa
86% sensitivity and 91% specificity

Treatment

• Lifestyle
  – Diet
  – Exercise

• Pharmacology
  – Vitamin E, pioglitazone
  – Liraglutide, obetacholic acid (OCA); elafibranor

• Bariatric surgery
Weight Loss Pyramid

- Fibrosis (45%)
- NASH Resolution (64-90%)*
- Ballooning/Inflammation (41-100%)*
- Steatosis (35-100%)*

*Depending on degree of weight loss
Bariatric Surgery

- Decreases Steatosis
- Decreases Inflammation / NASH
- No clear evidence of improvement in fibrosis
- Current Indication
  - BMI >40
  - >35 with comorbidity (DM, OSA, HTN, CHF)
- NAFLD currently not an indication for bariatric surgery but NASH is not contraindication
- Consider if multiple failed attempts at wt loss
- Acceptable surgical risk

Dixon Hepatology 2004
Furuya J Gastroenterol Hepatol 2007
Barker Am J Gastroenterol 2006
Chavez-Tapia Cochrane Database Sys Rev 2010
PIVENS Trial of Vitamin E or Pioglitazone in NASH:
Primary Endpoint: histologic improvement (↓ in NAS)

Primary endpoint = histologic improvement

Defined as: ≥1-point improvement in hepatocellular ballooning score, no increase in fibrosis score, and either a decrease in NAS to ≤3 or a ≥2-point decrease in NAS plus ≥1-point decrease in either the lobular inflammation or steatosis score

Abbreviations: NAS, nonalcoholic fatty liver disease score; NASH, nonalcoholic steatohepatitis, NNT, number needed to treat.

Effect of Pioglitazone on Liver Histology at 18 months*

*Primary: ≥2 point reduction in NAS without worsening fibrosis
*Secondary: resolution of NASH


Resolution of NASH defined as absence of NASH after 18 mo of therapy with definite NASH at baseline

* In patients with paired biopsies (n = 82)
Liraglutide for NASH (LEAN Trial)

**Primary Outcome (per protocol analysis)**

NASH on Biopsy
Non-DM or DM (not on insulin)

~33% had T2DM
HbA1c ~6.0
ALT ~70
~50% F0-2
~50% F3-4

- **Primary Outcome:**
  - Histology at week 48
  - Resolution of NASH + no worsening in fibrosis

![Graph showing comparison between Placebo and Liraglutide.]

- Placebo: N=22
- Liraglutide: N=23

P<0.05

Armstrong Lancet 2016;387:679
Obetacholic Acid: FLINT Primary Endpoint—Improved Liver Histology at Week 72

Histologic response: ≥2-point improvement in NAS without worsening of fibrosis

Abbreviations: NAS, nonalcoholic fatty liver disease activity score; OCA, obeticholic acid.
Elfibrinor: Primary Endpoint in ITT Population

Resolution of NASH Without Fibrosis Worsening

Protocol-defined (disappearance of steatosis or ballooning or lobular inflammation)

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo (n = 92)</th>
<th>ELF 80 mg (n = 93)</th>
<th>ELF 120 mg (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Rate</td>
<td>17</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>P-value</td>
<td>P = .28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified definition (no ballooning; lobular inflammation none or mild)

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<tr>
<th>Group</th>
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<th>ELF 120 mg (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Rate</td>
<td>12</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>P-value</td>
<td>P = .045</td>
<td></td>
<td></td>
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</table>

Abbreviations: EASL, European Association for the Study of the Liver; ELF, elafibrinor; ITT, intent-to-treat; NASH, nonalcoholic steatohepatitis.

Resolution of NASH: 
Comparison of Key NASH Therapies

*Statistically significant

Rates of resolution of NASH not available from cenicriviroc Phase 2 study (CENTAUR Trial); reported as no significant difference between treatment arms
Clinical Diagnosis of NAFLD
--overweight, insulin resistance, hepatic steatosis
--exclude HCV, HBV, ANA, meds, etc

Lifestyle Changes
Diet: ↓ calories, ↓ saturated fat
Exercise: 150 – 200 minutes/week

ALT significantly elevated or other concern

Biopsy

Not NAFLD
Treat appropriately

Fatty Liver
NASH NAS≤4
Lifestyle Changes Diet and Exercise

NASH NAS≥5
Vitamin E 800 IU/day

NASH + DM NAS≥5
Pioglitazone ± Vitamin E

NASH + BMI>35 + co-morbidities
Consider

Bariatric Surgery
Consider