NAFLD and NASH

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Overview

• Epidemiology and Natural History of NAFLD.
• Current Challenges:
  – 1. NAFLD is not a serious disease in young patients
  – 2. Screening is not indicated even in high-risk populations
  – 3. There is no FDA-approved treatment for NAFLD/Bariatric surgery cannot be recommended as Rx
• Discuss the management of NAFLD today.
NAFLD is the Hepatic Manifestation of Obesity/IR

Metabolic Syndrome
- Insulin Resistance
- Dyslipidemia
- Hypertension

NAFLD
NAFLD Prevalence

- **Adults**
  - Overall: ~30%
  - Obese: ~50-70%
  - Severely Obese: 85%
  - DM2: ~65-75%

- **Children**
  - Overall: ~10%
  - 15-19 years: ~17%
  - Obese: ~50%

The NAFLD Spectrum

NAFLD Activity Score

<table>
<thead>
<tr>
<th>Steatosis (0-3)</th>
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<tbody>
<tr>
<td>5-33%</td>
<td>1</td>
</tr>
<tr>
<td>34-65%</td>
<td>2</td>
</tr>
<tr>
<td>≥66%</td>
<td>3</td>
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<table>
<thead>
<tr>
<th>Inflammation (0-3)</th>
<th></th>
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<tbody>
<tr>
<td>&lt;2 under 20x</td>
<td>1</td>
</tr>
<tr>
<td>2-4 under 20x</td>
<td>2</td>
</tr>
<tr>
<td>&gt;4 under 20x</td>
<td>3</td>
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<table>
<thead>
<tr>
<th>Ballooning (0-2)</th>
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<tbody>
<tr>
<td>Few</td>
<td>1</td>
</tr>
<tr>
<td>Many</td>
<td>2</td>
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</table>

NAFL → NASH/Fibrosis → NASH Cirrhosis → HCC

80-100 Million
HCC in the Absence of Cirrhosis in US Veterans

Frequency of NASH as a Cause of Liver Transplantation in Adults

*HCV frequency was ≈ 45%

Burden of NAFLD Among Young Adults in the US

A Hospital-Based Cohort Study

n = 66 children with NAFLD, follow up for up to 20 years

2 patients developed NASH-cirrhosis that required LT at 20 and 25 years

LT for NASH in Children and Young Adults

NASH is the most rapidly increasing indication for OLT in young adults.
Current Screening for NAFLD: ALT and Ultrasonography

US Cannot Stage the Severity of Fibrosis in Patients with NAFLD

Staging the Severity of Steatosis and Fibrosis in NAFLD: VCTE + CAP
How Do I Manage My Patient with NAFLD

• 1. Rule out other etiologies of elevated ALT or fatty infiltration of the liver.
• 3. Assess Severity (NASH, advanced fibrosis)
• 4. Treatment:
  – Lifestyle
  – Pharmacologic
Assessment of the Severity of NAFLD
Algorithm for Assessing the Severity of NAFLD

Patient with NAFLD

NFS + VCTE

NFS < -1.455 and LSM < 7 kPa
- No advanced fibrosis
- Consider repeating every 2-3 years

Discordant results
- Liver Biopsy

NFS > 0.676 and LSM > 10 kPa
- Advanced fibrosis
- Screen for cirrhosis complications
- US every 6 months
Treatment: % Weight Loss Associated with Histological Improvement

Changing the Attitude Toward Healthy Lifestyle in Texas
Both Resistance Training and Aerobic Training Reduce Hepatic Fat Content

Weight Loss and NASH Improvement

Gastroenterology. 2015 Aug;149(2):367-78
Weight Loss and Fibrosis in NASH

Gastroenterology. 2015 Aug;149(2):367-78
Effects of Bariatric Surgery on Severe Liver Injury in Morbid Obese Patients with NASH

• 109 severely obese patients with biopsy-proven NAFLD had bariatric surgery

• Data were prospectively collected before and one year after surgery

• 64% gastric bypass, 29.4 gastric band

• BMI 49.3 \(\rightarrow\) 37.4 kg/m\(^2\)

Effects of Bariatric Surgery on Liver Histology

NASH Disappearance

NASH grade evolution (Brunt score)

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>NASH</td>
<td>11%</td>
<td>1.2%</td>
</tr>
<tr>
<td>No NASH</td>
<td>25.6%</td>
<td>9.8%</td>
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</table>

Comparison of NASH grade distribution p<0.00001

85% of NASH disappearance, 1 year after Bariatric surgery

Fibrosis Improvement

Fibrosis evolution

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>No NASH</td>
<td>85.4%</td>
<td>43.75%</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>3.75%</td>
<td>2.5%</td>
</tr>
<tr>
<td>0</td>
<td>3.7%</td>
<td>7.5%</td>
</tr>
<tr>
<td>1</td>
<td>9.8%</td>
<td>13.75%</td>
</tr>
<tr>
<td>2</td>
<td>27.5%</td>
<td>40%</td>
</tr>
<tr>
<td>3</td>
<td>21.25%</td>
<td>7.5%</td>
</tr>
<tr>
<td>4</td>
<td>2.5%</td>
<td>7.5%</td>
</tr>
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p<0.003

*Metavir scale.
Significant improvement of Fibrosis lesions 1 year after bariatric surgery.

N= 82 patients with paired liver biopsies
# Endpoints in NASH Trials

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<thead>
<tr>
<th>Trial Phase</th>
<th>Primary</th>
<th>Secondary</th>
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<tbody>
<tr>
<td>Phase I/II</td>
<td>• MRI-PDFF</td>
<td>• Decline in ALT</td>
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<tr>
<td></td>
<td>• ALT</td>
<td>• Decline in CK18</td>
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<tr>
<td></td>
<td>• Decline in ALT</td>
<td>• Change in MRE</td>
</tr>
<tr>
<td></td>
<td>• Decline in CK18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Change in MRE</td>
<td></td>
</tr>
<tr>
<td>Phase II/III</td>
<td>• Liver histology: NAS; resolution of NASH; improvement in fibrosis; delayed progression</td>
<td>• MRI-PDFF/MRE</td>
</tr>
<tr>
<td></td>
<td>• HVPG</td>
<td>• Decline in ALT</td>
</tr>
<tr>
<td></td>
<td>• Clinical outcomes</td>
<td>• Decline in ALT</td>
</tr>
<tr>
<td></td>
<td>• MELD</td>
<td>• Decline in CK-18</td>
</tr>
<tr>
<td>Phase IV</td>
<td>Long-term clinical outcomes</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; CK18, cytokeratin-18; HVPG, hepatic venous pressure gradient; MELD, Model for End-Stage Liver Disease; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-derived proton density-fat fraction; NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis. Graphic courtesy of Rohit Loomba, MD.
Phase III PIVENS Trial of Vitamin E or Pioglitazone in NASH—Primary Endpoint

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

Vitamin E 800 IU/day: 43 patients met endpoint, NNT = 4.2
Placebo: 19 patients met endpoint, NNT = 6.9
Pioglitazone 30 mg/day: 34 patients met endpoint, NNT = 6.9

Abbreviations: NAS, nonalcoholic fatty liver disease score; NASH, nonalcoholic steatohepatitis, NNT, number needed to treat.
Phase IIb FLINT Trial of Obeticholic Acid in NASH—Primary Endpoint

Primary endpoint = histologic response

Defined as ≥2-point improvement in NAS and no worsening of fibrosis

Abbreviations: NAS, nonalcoholic fatty liver disease score; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid. Neuschwander-Tetri BA, et al. Lancet. 2015;385:956-965.
Cenicriviroc Efficacy at 52 Weeks (CENTAUR)

- Dual inhibitor of C-C chemokine receptor 2 & 5 (CCR2/ CCR5)
- Phase IIb trial of 289 patients with NASH (NAS ≥ 4), liver fibrosis, DM/ MetS

Selonsertib: Short-Term Efficacy at 24-Weeks

- Apoptosis signal-regulating kinase (ASK1) inhibitor.
- Phase II trial of patients with biopsy-confirmed NASH, NAS ≥ 5, F2-F3 liver fibrosis (N = 72)

Gut Microbiome in NAFLD and NASH

Abbreviations: CCL, chemokine ligand; EtOH, ethanol; FFA, free fatty acids; Fiaf, fasting-induced adipocyte factor; HFD, high-fat diet; IL, interleukin; LPL, lipoprotein lipase; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NLRP, nucleotide-binding domain, leucine-rich repeat protein; SCFA, short-chain fatty acids; TMA, trimethylamine; VLDL, very-low-density lipoproteins.

Summary

• NASH has along natural history
• Many confounding factors in clinical outcomes
  – Cardiovascular disease
  – Diabetes
  – Cancer
  – Weight loss
• Surrogate Endpoints Needed
• Evolution from NASH resolution to fibrosis improvement
• Blended endpoints to combine clinical benefit, surrogate markers