NAFLD- A Growing Problem

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Background

- NAFLD is present 20-30% of Adults in the west
  - 10-15% in children
  - By MRI in general population 35% & by CT/US ~ 15-17%
  - By ALT/AST ~ 7%

- Most common cause of elevated liver enzymes in both adults and children

- Expected to become the most common indication for Liver transplantation by 2030

Tapper. NAT REV GASTRO & HEPAT 2018
Modeling the Epidemic of Nonalcoholic Fatty Liver Disease Demonstrates an Exponential Increase in Burden of Disease

Prevalent NAFLD cases forecasted to increase by 21%, 83.1 million 2015-100.9 million 2030

NASH projected to increase 63% from 16.52 million cases in 2015 to 27.00 million in 2030
Modeling the Epidemic of Nonalcoholic Fatty Liver Disease Demonstrates an Exponential Increase in Burden of Disease

Incidence of decompensated cirrhosis will increase by 168% to 105,430 cases.
Incidence of HHC will increase by 137% to 12,240 cases.
Liver related deaths Increase of 178% to 78,300 cases.
When the journey from obesity to cirrhosis takes an early start

Marchesini. J Hepatol 2016
Hepatic outcome of NAFLD

Mortality increases with fibrosis

Systematic Review and Meta-Analysis of 5 studies:
1495 NAFLD patients with 17,452 py follow-up

- 38% Cardiovascular disease
- 19% Non-liver malignancy
- 8% Liver diseases
- 1% HCC
- <1% Liver transplantation
- 8% Infections
- 8% Others 8-18%

All-Cause Mortality

<table>
<thead>
<tr>
<th>Fibrosis stage</th>
<th>Mortality rate (per 1,000 PYF)</th>
<th>MRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>15.2</td>
<td>Reference</td>
</tr>
<tr>
<td>Stage 1</td>
<td>17.1</td>
<td>1.58 (1.19-2.11)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>27.9</td>
<td>2.52 (1.85-3.42)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>36.0</td>
<td>3.48 (2.51-4.83)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>45.8</td>
<td>6.40 (4.11-9.95)</td>
</tr>
</tbody>
</table>

Liver-Related Mortality

<table>
<thead>
<tr>
<th>Mortality rate (per 1,000 PYF)</th>
<th>MRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Reference</td>
</tr>
<tr>
<td>0.30</td>
<td>0.64</td>
</tr>
<tr>
<td>Stage 1</td>
<td>4.28</td>
</tr>
<tr>
<td>Stage 2</td>
<td>7.92</td>
</tr>
<tr>
<td>Stage 3</td>
<td>23.3</td>
</tr>
<tr>
<td>Stage 4</td>
<td>42.30</td>
</tr>
</tbody>
</table>

Dulai. HEPATOLOGY 2017; Angulo. Gastroenterol 2015
Spectrum of NAFLD

Simple Steatosis

12-40%

NASH without severe fibrosis (F1-F2)

19-22%
15-43%

NASH with severe fibrosis (F3)

38-50%

Cirrhosis

1% rapid progression

8-16% rapid progression

8% rapid progression

Sanjal 2010
Younousi 2018
Pais 2013
McPherson 2015
Singh 2015
Risk-factors for NAFLD/Progression

Established Associations

• Type II DM
• Dyslipidemia
• Central Obesity
• **PCOS (44% histologic NASH)**
• Metabolic syndrome (MetS)
  “Hepatic component”

Emerging Associations

• Hypothyroidism
• **Obstructive Sleep Apnea**
• Hypopituitarism
• Hypogonadism
• Hereditary (**1st degree 13x**)
• Psoriasis

Carriers of the PNPLA3 I148M and the TM6SF2 E167K variants: higher liver fat content and increased risk of NASH. Not systemically associated with features of insulin resistance.
Pathogenesis of NAFLD: “multi-hit” hypothesis

- Insulin Resistance
  - Metabolic Syndrome
    - Steatosis
      - ↑TGF-β
      - ↑TNF-α
      - ↓adiponectin
      - ↑oxidative damage
      - ↓glutathione
dysregulated apoptosis

- NASH
  - ↑hepatocyte death
  - ↑stellate cell activity/TGF-β

- Fibrosis
  - ↓hepatic regeneration
  - abnormal hepatocyte repair
Acetyl-CoA carboxylase (ACC) is fundamental in the pathophysiology of NASH

- Increase *de novo* lipogenesis (DNL) is pathogenic in NASH
- Acetyl-CoA carboxylase (ACC) catalyses the rate limiting step in DNL
- In pre-clinical models, ACC-inh improves steatosis, inflammation & fibrosis

Loomba. AASLD 2017; Lambert gastroenterol 2015
Farnesoid X receptor (FXR) agonists: Proposed mechanism in NASH

- ↓ Bile acid synthesis
- ↓ Lipogenesis
- ↓ Gluconeogenesis
- ↑ Beta Oxidation
- ↑ Glucogen synthesis

FXR
FGF-19
FGFR4
Bile acids

Nat Rev Drug Discover 2016
Work up of patients with NAFLD

• Imaging to document steatosis
• Alcohol and medication history
• Exclusion of other etiologies
• Auto-antibodies and ↑ Ferritin
• Fasting profile and insulin levels
• Liver enzymes can be NORMAL!!
Non-Invasive Tests

Two different but complementary approaches

**Biological approach**
- AST/ALT ratio
- APRI
- FIB-4
- FibroTest
- ELF
- FibroMetre

**Physical approach**
- BARD score
- NAFLD score (NFS)

Serum biomarkers

CAP/TE

MRE

Younossi. Hepatology. 2017
Treatment
## Treatment Goals

**Resolution of NASH, Improvement in Fibrosis**

*reducing Cirrhosis and HCC*

<table>
<thead>
<tr>
<th>AGENTS TESTED</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Certainly works</strong></td>
<td>Weight loss (diet, exercise, surgery)</td>
</tr>
<tr>
<td></td>
<td>Thiazolidinediones (Piog, Rosig.)</td>
</tr>
<tr>
<td></td>
<td>Vitamin E (non-DM)</td>
</tr>
<tr>
<td><strong>Certainly DON’T work</strong></td>
<td>UDCA</td>
</tr>
<tr>
<td></td>
<td>Metformin</td>
</tr>
<tr>
<td></td>
<td>Orlistat</td>
</tr>
<tr>
<td></td>
<td>Milk Thistle</td>
</tr>
<tr>
<td></td>
<td>Omega-3 fatty acids</td>
</tr>
<tr>
<td><strong>Promising but too soon to tell</strong></td>
<td>Obeticholic Acid (FXR)</td>
</tr>
<tr>
<td></td>
<td>Elafibranor (PPAR)</td>
</tr>
<tr>
<td></td>
<td>Liraglutatide (GLP-1)</td>
</tr>
<tr>
<td></td>
<td>Cenicriviroc</td>
</tr>
<tr>
<td></td>
<td>Pentoxifylline</td>
</tr>
<tr>
<td><strong>Phase 1, 2, 3 clinical trials</strong></td>
<td>&gt; 50 compounds</td>
</tr>
</tbody>
</table>
Weight loss as a treatment for NAFLD

Recommended for ALL

- Reduce calorie intake, life-style changes, exercise (vigorous), pharmacological, and surgical options are explored
- Consistent biochemical and histological benefits if weight loss > 7-10% body weight
- No available data for Fad diets (Atkins, south beach,.....)
Weight loss through life-style modification and impact on NASH

• N=293 with biopsy-proven NASH underwent life-style modification for 52 weeks
• N=261 follow up biopsies
• at 52 weeks, weight loss >5% achieved in 30% of subjects
• The magnitude of weight loss was independently associated with improvement in histology

Vilar-Gomez et al. Gastroenterology 2015
## Improvement of histologic outcomes

<table>
<thead>
<tr>
<th>Variables</th>
<th>WL &lt;5 (n=205)</th>
<th>WL 5-6.99 (n=34)</th>
<th>WL 7-9.99 (n=25)</th>
<th>WL ≥ 10 (n=29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution of NASH</td>
<td>21 (10)</td>
<td>9 (26)</td>
<td>16 (64)</td>
<td>26 (90)</td>
<td>P&lt; 0.01</td>
</tr>
<tr>
<td>NAS improvement</td>
<td>66 (32)</td>
<td>9 (26)</td>
<td>16 (64)</td>
<td>26 (90)</td>
<td>P&lt; 0.001</td>
</tr>
<tr>
<td>Steatosis improvement</td>
<td>72 (35)</td>
<td>22 (65)</td>
<td>19 (76)</td>
<td>29 (100)</td>
<td>P&lt; 0.001</td>
</tr>
<tr>
<td>Lob. Inflammation</td>
<td>72 (35)</td>
<td>24 (71)</td>
<td>22 (88)</td>
<td>29 (100)</td>
<td>P&lt; 0.001</td>
</tr>
<tr>
<td>Ballooning improvement</td>
<td>54 (26)</td>
<td>14 (41)</td>
<td>21 (84)</td>
<td>26 (90)</td>
<td>P&lt; 0.001</td>
</tr>
<tr>
<td>Fibrosis status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regression</td>
<td>33 (16)</td>
<td>6 (18)</td>
<td>4 (16)</td>
<td>13 (45)</td>
<td>P&lt; 0.01</td>
</tr>
<tr>
<td>Stabilization</td>
<td>129 (63)</td>
<td>25 (74)</td>
<td>21 (84)</td>
<td>16 (55)</td>
<td></td>
</tr>
</tbody>
</table>

Vilar-Gomez et al. Gastroenterology 2015
Significant improvement in Histology following Bariatric surgery

- Bariatric surgery improves steatosis, necroinflammation, fibrosis
- Meta-analysis by Mummadi et al. improve HS, NASH, fibrosis post-bariatric surgery

Significant improvement in Histology following Bariatric surgery

Significant improvement in fibrosis
## Thiazolidinediones (TZD) for NASH

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Agent</th>
<th>Duration</th>
<th>Enzymes</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetri</td>
<td>30</td>
<td>Rosig 8mg</td>
<td>48 weeks</td>
<td>Improved</td>
<td>Improved steatosis, inflammation &amp; fibrosis</td>
</tr>
<tr>
<td>Sanyal</td>
<td>21</td>
<td>Piog 30mg</td>
<td>6 months</td>
<td>N/A</td>
<td>Improved steatosis, inflammation</td>
</tr>
<tr>
<td>Belfort</td>
<td>55</td>
<td>Piog 45mg</td>
<td>6 months</td>
<td>Improved</td>
<td>Improved steatosis, inflammation</td>
</tr>
<tr>
<td>Ratziu</td>
<td>63</td>
<td>Rosig 8mg</td>
<td>12 month</td>
<td>Improved</td>
<td>Improved steatosis</td>
</tr>
<tr>
<td>Aithal</td>
<td>74</td>
<td>Piog 30m</td>
<td>12 months</td>
<td>Improved</td>
<td>Improved steatosis, inflammation &amp; fibrosis</td>
</tr>
<tr>
<td>PIVENS</td>
<td>247</td>
<td>Piog 30mg</td>
<td>24 months</td>
<td>Improved</td>
<td>Improved steatosis, inflammation, fibrosis &amp; Ballooning</td>
</tr>
</tbody>
</table>
Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

339 Patients were assessed for eligibility

- 92 Were excluded
  - 82 Did not meet inclusion criteria
  - 7 Declined to participate
  - 3 Had other reasons

247 Underwent randomization

- 83 Were assigned to receive placebo
- 84 Were assigned to receive vitamin E
- 80 Were assigned to receive pioglitazone
PIVENS Trial

Table 2. Primary Outcome and Changes in Histologic Features of the Liver after 96 Weeks of Treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Vitamin E</th>
<th>Pioglitazone</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects randomly assigned</td>
<td>83</td>
<td>84</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Subjects with improvement (%)</td>
<td>19</td>
<td>43</td>
<td>34</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

*P Value for comparison between Vitamin E vs. Placebo and Pioglitazone vs. Placebo.
TZDs for NASH: Meta-analysis

• Consistently Positive effect on Liver Histology
  • Steatosis OR 4.05
  • Inflammation OR 3.53
  • Fibrosis OR 1.04

• Weight gain 2-5 kg (~60-70% of patients)

• Pio better than Rosi

• Responders ~45%
  • histological benefits lost upon D/C

• Bone fractures, ??CV, Carcinogenesis (bladder)

Musso et al. Hepatology 2010
**Statins** can be used **SAFELY** in NAFLD

- Patients with NAFLD are important targets for Statins
- Risk of hepato-toxicity from statins is very rare
- Patients with underlying liver disease are **NOT** at higher risk of hepatotoxicity from statins
- Case series have shown histologic improvement with statins

Sigler Clin Med Insights Gastroenterol. 2018
After adjusting for age, race and BMI, Statins lower risk of having advanced fibrosis (Atorva/Simva)

<table>
<thead>
<tr>
<th>Anti-Lipid Agent</th>
<th>Adjusted OR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Lipid Medications</td>
<td>0.63</td>
<td>0.017</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>0.58</td>
<td>0.021</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>0.57</td>
<td>0.029</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>0.65</td>
<td>0.24</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>0.62</td>
<td>0.24</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>0.84</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Sigler. Clin Med Insights Gastroenterol. 2018
Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial

Brent A Neuschwander-Tetri, Rohit Loomba, Arun J Sanyal, Joel E Lavine, Mark L Van Natta, Manal F Abdelmalek, Naga Chalasani, Srinivasan Dasarathy, Anna Mae Diehl, Bilal Hameed, Kris V Kowdley, Arthur McCullough, Norah Terrault, Jeanne M Clark, James Tonascia, Elizabeth M Brunt, David E Kleiner, Edward Doo, for the NASH Clinical Research Network*

- **N=283 OCA 25mg PO daily vs. Placebo**
  - Inclusion: Biopsy-proven NASH, NAS≥ 4
  - Exclusion: Cirrhosis
- **N= 283 patients for 72 weeks**
- **Biopsies <3 months and after 72 weeks**
- **Primary endpoints:**
  - Improvement in NAFLD activity score > 2
  - No worsening of fibrosis

*Neuschwander-Tetri et al. Lancet Nov 2015*
# The FLINT Trial

<table>
<thead>
<tr>
<th></th>
<th>Obeticholic acid</th>
<th>Placebo</th>
<th>Relative risks or mean changes from baseline* (95% CI) (obeticholic acid vs placebo)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients at risk‡</td>
<td>110</td>
<td>109</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>50 (45%)</td>
<td>23 (21%)</td>
<td>2.2 (1.4 to 3.3)</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>Changes from baseline in histological features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with biopsy specimens at baseline and 72 weeks</td>
<td>102</td>
<td>98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution§ of definite non-alcoholic steatohepatitis</td>
<td>22 (22%)</td>
<td>13 (13%)</td>
<td>17 (0.9 to 3.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>Fibrosis¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>36 (35%)</td>
<td>19 (19%)</td>
<td>2.0 (1.2 to 3.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Change in score</td>
<td>−0.2 (1.0)</td>
<td>0.1 (0.9)</td>
<td>−0.3 (−0.6 to −0.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total NAFLD activity score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in score</td>
<td>−1.7 (1.8)</td>
<td>−0.7 (1.8)</td>
<td>−0.9 (−1.3 to −0.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hepatocellular ballooning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>47 (46%)</td>
<td>30 (31%)</td>
<td>1.5 (1.0 to 2.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Change in score</td>
<td>−0.5 (0.9)</td>
<td>−0.2 (0.9)</td>
<td>−0.2 (−0.5 to 0.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Steatosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>62 (61%)</td>
<td>37 (38%)</td>
<td>1.6 (1.2 to 2.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in score</td>
<td>−0.8 (1.0)</td>
<td>−0.4 (0.8)</td>
<td>−0.4 (−0.6 to −0.2)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Lobular inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>54 (53%)</td>
<td>34 (35%)</td>
<td>1.6 (1.1 to 2.2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Change in score</td>
<td>−0.5 (0.8)</td>
<td>−0.2 (0.9)</td>
<td>−0.3 (−0.5 to −0.1)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Portal inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with improvement</td>
<td>12 (12%)</td>
<td>13 (13%)</td>
<td>1.0 (0.5 to 2.2)</td>
<td>0.90</td>
</tr>
<tr>
<td>Change in score</td>
<td>0.2 (0.7)</td>
<td>0.2 (0.7)</td>
<td>0.0 (−0.1 to 0.2)</td>
<td>0.59</td>
</tr>
</tbody>
</table>
Adverse Events

• 6 severe adverse events OCA
  • Pruritis (1 had to stop)
  • 1 hypoglycemia
  • 1 possible cerebral ischemia (dysarthria, dizziness)

• Moderate or Severe Pruritis
  • 23% in OCA
  • 6% in Placebo

39% of patients who received liraglutide and underwent end-of-treatment liver biopsy had resolution of NASH compared to 9% of patients in the placebo group.

9% patients in the liraglutide group versus 36% of patients in the placebo group had progression of fibrosis.
### Phase 2 Elafibranor (GOLDEN-505)

**PPAR alpha-delta agonist**

Elafibranor 120mg has significant effect vs. placebo in both global and NAS ≥4 populations.

<table>
<thead>
<tr>
<th>N</th>
<th>NAS</th>
<th>Placebo</th>
<th>Elafibranor 120mg</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>274</td>
<td>All patients (FAS)</td>
<td>12%</td>
<td>19%</td>
<td>0.045</td>
</tr>
<tr>
<td>234</td>
<td>NAS≥4</td>
<td>9%</td>
<td>19%</td>
<td>0.013</td>
</tr>
<tr>
<td>204</td>
<td>NAS≥4 with fibrosis (any stage)</td>
<td>11%</td>
<td>20%</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Resolution of NASH without worsening of fibrosis

*Ratziu. Gastroenterology 2016*
Phase 2 Elafibranor (GOLDEN-505)

**PPAR alpha-delta agonist**

- Significant improvement in Glucose & lipid profile
- No change in body weight
- Good safety profile

*Patients with resolved NASH significant reduction in fibrosis*

*Ratziu. Gastroenterology 2016*
A Randomized, Placebo-Controlled Trial of Cenicriviroc for Treatment of NASH With Fibrosis

CENTAUR 1 year result

- CVC showed a significant antifibrotic benefit at year 1 and was well tolerated
- Although the primary endpoint was not met, CVC provided clinically meaningful benefits and resulted in twice as many subjects achieving “improvement in fibrosis by 1 stage”

Friedman. HEPATOLOGY 2018
A Randomized, Placebo-Controlled Trial of Cenicriviroc for Treatment of NASH With Fibrosis

**CENTAUR 2 year result (Phase 2b)**

Improvement in fibrosis by ≥ 2 stages AND no worsening of NASH from baseline at 2 years

- **N=35** Placebo: 3%
- **N=65** Cenicriviroc: 11%

**Durability of antifibrotic response**

- CVC was well tolerated and provided antifibrotic activity in NASH fibrosis
- Twice CVC-treated patients achieving ≥1 stage improvement at year 1 maintained this benefit at year 2 particularly in stage 3 fibrosis

*Ratziu. ILC 2018, GS-002*
## Phase III Therapeutic trails in NASH

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESOLVE-IT</td>
<td>NASH + NAS &gt; 4 + F2/3</td>
</tr>
<tr>
<td>REGENERATE</td>
<td>NASH + NAS &gt; 4 + F2/3</td>
</tr>
<tr>
<td>STELLAR 3</td>
<td>NASH + NAS &gt; 4 + F3/4</td>
</tr>
<tr>
<td>AURORA</td>
<td>NASH + F2/3</td>
</tr>
</tbody>
</table>
Take home messages

• NASH is progressive and can lead to Cirrhosis
  • Excluding competing etiologies and co-existing liver disease
• NAFLD patients are at higher risk of DM-II, CVD disease, All-cause mortality
• Liver biopsy can establish the diagnosis of NASH, Non-invasive tests for fibrosis
• Management of NAFLD include managing metabolic syndrome as well as managing liver disease
THANK YOU
Worldwide estimated prevalence of NAFLD