Non-Alcoholic Steatohepatitis: What Is It and How Do We Treat and Monitor?

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It is Important to Know that NASH is a Part of the Spectrum of NAFLD with Differential Progression

- NASH requires specific pathologic criteria
- Exclusion of liver diseases
- Important for prognosis

Global Epidemiology of NAFLD

Meta-analytic Assessment of Prevalence, Incidence and Outcomes

- Pubmed and MEDLINE databases were searched from 1989-2015 for terms involving epidemiology and progression of NAFLD.
- Out of 729 studies, **86 were included with a sample size of 8,515,431 from 22 countries**
- Global prevalence of NAFLD is 25.24% (22.10-28.65) with highest prevalence in Middle East and South America and lowest in Africa

Younossi Z et al. Hepatology 2015
The Global Prevalence of NAFLD

North America: 24.13%
Europe: 23.71%
South America: 30.45%
Africa: 13.48%
Middle East: 31.79%
Asia: 27.37%

Younossi Z et al. Hepatology 2015
## Risk Factors for NAFLD

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Continent &amp; Referral Status</th>
<th>N</th>
<th>Prevalence (%)</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Europe, Referral</td>
<td>1</td>
<td>89.19</td>
<td>(74.51 - 95.88)</td>
</tr>
<tr>
<td></td>
<td>North America, Random or Voluntary</td>
<td>1</td>
<td>80.00</td>
<td>(64.83 - 89.67)</td>
</tr>
<tr>
<td></td>
<td>Oceania, Referral</td>
<td>1</td>
<td>95.24</td>
<td>(82.86 - 98.81)</td>
</tr>
<tr>
<td></td>
<td>South America, Referral</td>
<td>1</td>
<td>45.45</td>
<td>(26.47 - 65.86)</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>4</td>
<td>81.83</td>
<td>(55.16 - 94.28)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>North America, Random or Voluntary</td>
<td>1</td>
<td>25.00</td>
<td>(14.01 - 40.54)</td>
</tr>
<tr>
<td></td>
<td>North America, Referral</td>
<td>5</td>
<td>54.09</td>
<td>(37.26 - 70.04)</td>
</tr>
<tr>
<td></td>
<td>Oceania, Referral</td>
<td>1</td>
<td>35.71</td>
<td>(22.81 - 51.08)</td>
</tr>
<tr>
<td></td>
<td>South America, Referral</td>
<td>1</td>
<td>36.36</td>
<td>(19.34 - 57.67)</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>9</td>
<td>43.63</td>
<td>(30.28 - 57.98)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>North America, Referral</td>
<td>1</td>
<td>83.07</td>
<td>(79.92 - 85.81)</td>
</tr>
<tr>
<td></td>
<td>Oceania, Referral</td>
<td>1</td>
<td>61.90</td>
<td>(46.57 - 75.18)</td>
</tr>
<tr>
<td></td>
<td>South America, Referral</td>
<td>1</td>
<td>63.64</td>
<td>(42.33 - 80.66)</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>3</td>
<td>72.13</td>
<td>(54.59 - 84.78)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>North America, Referral</td>
<td>1</td>
<td>83.33</td>
<td>(36.87 - 97.72)</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>1</td>
<td>83.33</td>
<td>(36.87 - 97.72)</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>North America, Referral</td>
<td>1</td>
<td>70.65</td>
<td>(54.64 - 82.79)</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>2</td>
<td>70.65</td>
<td>(54.64 - 82.79)</td>
</tr>
</tbody>
</table>

Although the vast majority of NAFLD patients are overweight or obese, there is group of lean patients with NAFLD

Younossi Z et al. Hepatology 2015
Although Most Cases are in Obese/Overweight, Lean Individuals Can Also Have NAFLD

- 11,613 NHANES-III participants
- NAFLD was defined as fat by US, no ETOH and other CLD
- Prevalence of NAFLD in obese and OW: 17.7%
- Prevalence of NAFLD in lean individuals (BMI<25): 3.7%
- Compared to OB/OW NAFLD, lean NAFLD is younger, more female, less IR and have lower AST and ALT
- Compared to their own controls, lean NAFLD has more IR and DM

<table>
<thead>
<tr>
<th>Lean (BMI&lt;25)</th>
<th>Overweight or obese (BMI&gt;25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD (N=431)</td>
<td>Control (N=4026)</td>
<td>NAFLD (N=2061)</td>
</tr>
<tr>
<td>W, %</td>
<td>72.48 ± 4.51</td>
<td>79.17 ± 1.99</td>
</tr>
<tr>
<td>AA, %</td>
<td>10.25 ± 2.08</td>
<td>8.34 ± 0.92</td>
</tr>
<tr>
<td>His%,</td>
<td>6.97 ± 1.64 *</td>
<td>4.15 ± 0.68</td>
</tr>
<tr>
<td>Othe%,</td>
<td>10.30 ± 3.10</td>
<td>8.35 ± 1.24</td>
</tr>
<tr>
<td>Male%</td>
<td>43.57 ± 4.03</td>
<td>42.24 ± 1.14</td>
</tr>
<tr>
<td>VO, %</td>
<td>8.05 ± 1.69 *</td>
<td>4.45 ± 0.40</td>
</tr>
<tr>
<td>IR, %</td>
<td>13.35 ± 2.41 *</td>
<td>6.03 ± 0.48</td>
</tr>
<tr>
<td>DM, %</td>
<td>6.72 ± 1.41 *</td>
<td>1.34 ± 0.25</td>
</tr>
<tr>
<td>HCh%,</td>
<td>62.65 ± 3.80 *</td>
<td>53.77 ± 1.44</td>
</tr>
<tr>
<td>HTN%,</td>
<td>17.83 ± 2.39 *</td>
<td>10.46 ± 0.56</td>
</tr>
<tr>
<td>Age</td>
<td>41.94 ± 1.15 *</td>
<td>39.61 ± 0.43</td>
</tr>
<tr>
<td>BMI</td>
<td>22.17 ± 0.16</td>
<td>22.09 ± 0.04</td>
</tr>
<tr>
<td>HOMA</td>
<td>2.77 ± 0.33 *</td>
<td>1.67 ± 0.05</td>
</tr>
<tr>
<td>ALT</td>
<td>17.96 ± 0.98 *</td>
<td>14.25 ± 0.27</td>
</tr>
<tr>
<td>AST</td>
<td>21.50 ± 0.60 *</td>
<td>19.57 ± 0.16</td>
</tr>
</tbody>
</table>

Younossi Z et al. Medicine 2012
Despite Being Very Common, NAFLD is Not Well Recognized in Clinical Practice

- Houston VA patients (2001–2011) with chronic elevation of ALT and no liver diseases (n = 19,692)
- Random sample (n = 450)
- Structured chart review to confirm the criteria for NAFLD and metabolic syndrome
- Data from the primary care providers’ notes were abstracted for
  - Recognition of abnormal ALT levels
  - Mention of NAFLD as a possible diagnosis
  - Recommendations for diet or exercise
  - Referral to a specialist for NAFLD evaluation

Of patients with NAFLD (N=251)
- 39.4% recognition of ALT increase
- 21.5% diagnosed possible NAFLD
- 14.7% received recommendation for lifestyle changes
- 10.4% were referred to a specialist
- Of those at high risk for fibrosis, 3% were referred to specialists

NASH is the Subtype of NAFLD the Primarily Progresses

NAFL

NAFLD

NASH

Stable

Cirrhosis

Liver Failure

HCC

(Annual incidence 2%)

Stable

Death

10-15%

65-75%

40-60%

20-30%

Predictors of Progressive Liver Disease and Mortality
What Are the Clinical Predictors of Advanced Fibrosis In NAFLD?

- NAFLD with liver biopsy (N=432)
- In multivariate analysis, elevated AST and ALT, presence of diabetes mellitus, male gender and Caucasian ethnicity were associated with moderate to severe fibrosis (p<0.0001)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Advanced Fibrosis OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.61 (1.21-2.01)</td>
<td>0.0374</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.64 (1.13-2.17)</td>
<td>0.0258</td>
</tr>
<tr>
<td>HTN and DM</td>
<td>1.69 (1.11-2.28)</td>
<td>0.0246</td>
</tr>
<tr>
<td>HTN+DM+VO</td>
<td>1.72 (1.13-2.31)</td>
<td>0.0205</td>
</tr>
</tbody>
</table>

Hossain N, et al Gastro and Hepatology 2009
What Are the Clinical Predictors of Mortality In NAFLD?

- Histologic NAFLD (N=289)
- Clinico-demographic data from biopsy date
- NASH (59.2%), non-NASH (40.8%)
  - NASH patients were predominantly female, higher AST, ALT and serum glucose
- Mortality: Median follow-up of 150 months
  - NASH had higher risk of liver-related mortality than non-NASH NAFLD (p= 0.002).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Overall mortality aHR (95% CI)</th>
<th>Liver-related mortality aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH</td>
<td>1.13 (0.74 - 1.71)</td>
<td>9.16 (2.10 - 9.88)</td>
</tr>
<tr>
<td>Age</td>
<td>1.07 (1.05 - 1.10)</td>
<td>1.06 (1.02 - 1.10)</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.95 (0.62 - 1.47)</td>
<td>1.44 (0.62 - 3.34)</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>1.67 (0.92 - 3.06)</td>
<td>1.85 (0.62 - 5.47)</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.91 (0.60 - 1.40)</td>
<td>0.88 (0.38 - 2.04)</td>
</tr>
<tr>
<td>DM</td>
<td>2.09 (1.39 - 3.14)</td>
<td>2.19 (1.00 - 4.81)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.01 (0.68 - 1.52)</td>
<td>0.48 (0.19 - 1.23)</td>
</tr>
</tbody>
</table>
What Are the Histologic Predictors of Mortality In NAFLD?

- NAFLD liver biopsy and mortality data (N=209)
- Biopsies were read centrally
- During follow-up (146 months), 31% of patients died with 9% dying of LRM
- Despite the pathologic protocol, NASH had higher LRM than non-NASH NAFLD
  - 13.0% vs. 1.3%, p = 0.0047

Univariate survival analyses
[HR (95% CI) , p-value]

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal inflam (grade≥2)</td>
<td>6.68 (2.20-20.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ballooning (grade≥2)</td>
<td>5.32 (1.89-14.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>MD bodies (grade≥2)</td>
<td>4.21 (1.66-10.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Portal fib (grade&gt;2)</td>
<td>14.1 (5.47-36.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pericellular fib (grade&gt;2)</td>
<td>4.86 (1.73-13.7)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

On multivariate analysis, only significant fibrosis (grade > 2) was an independent predictor of LRM

Multivariate Analysis

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.4 (0.63, 8.91)</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>7.5 (2.26, 24.94)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3</td>
<td>13.8 (4.35, 43.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>47.5 (11.94, 188.61)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NAFLD and HCC

- Several case reports and case series of well documented cases of HCC in NAFLD patients
- NAFLD is the third most common cause of HCC
  - Cumulative incidence of HCC in NASH cirrhosis is 2.6% as compared to 4% in HCV
- Characteristics:
  - More males (73%), average age 67
  - Single lesion (76%) well to moderately differentiated
  - Larger tumors than viral hepatitis and ALD
    - 12.8 cm vs. 8.8 cm vs. 7.7 cm (p=0.001)

NAFLD and HCC

- HCC (N=4979) (SEER 2004–2009) & 14937 non-HCC
- Number of HCC cases increased between 2004-2009

- NAFLD-HCC (n=145) and HCV-HCC (n=611)
- NAFLD-HCC: More metabolic condition, larger tumor & infiltrative pattern
- NAFLD-HCC found often outside surveillance
- Cirrhosis in 50% of NAFLD-HCC & all HCV-HCC
- Regardless of tumor stage, survival was significantly shorter (P=0.017) in patients with NAFLD-HCC [25.5 months (21.9-29.1)] than in those with HCV-HCC [33.7 months (31.9-35.4)]

With 1-yr of Dx, fewer HCV/HBV than NAFLD (53% vs. 61%, p<0.05)

Age, ESRD, advanced HCC, disease severity, ALD (HR 1.27 (1.06-1.54), NAFLD 1.21 (1.01-1.45) were independently associated with mortality within 1-yr of Dx

Overall survival

After controlling for confounders, the mean survival was no longer different

HCC in Non-Cirrhotic Patients

- 1500 VA patients & HCC (2005-2010)
- Patients without cirrhosis were assigned into 2 categories
  - 43/1500 HCC (2.9%) level 1 evidence no cirrhosis (very high prob)
  - 151/1500 (10.1%) level 2 evidence no cirrhosis (high prob)
- Risk of having HCC in the absence of cirrhosis
  - NAFLD: Unadj OR: 5.4; 95% CI (3.4–8.5)
  - MS: Unadj OR: 5.0; 95% CI (3.1–7.8)

About 13% of patients with HCC in the VA system do not have cirrhosis. NAFLD and MS are main risk factors for HCC in the absence of cirrhosis.
NAFLD and OLT

- OPTN (2004-2013) LT list
  - New waitlist for NASH increased by 170%
  - ALD increased by 45%
  - HCV increased by 14%
- NASH has become the 2nd indication for LT listing (2013)
- 90 day on the list mortality:
  - ALD lower than NASH: OR: 0.77; 0.67–0.89; P < .001
  - NASH similar to HCV
- Compared to HCV, NASH patients had the lowest chance of getting transplanted in 90 days and 1 year

Pathogenic Pathways of NASH
NASH Pathogenesis—Multiple-Hit Hypothesis

1st Hit
- Increased lipolysis and increased delivery of FFA to liver
- Results in steatosis and accumulation of liver fat

2nd Hit
- Oxidative stress from mitochondrial ROS and CYP-450 enzymes
- Alternative 2nd hit: adipokines associated with obesity and factors associated with apoptotic pathway
  - Results in inflammation and necrosis

Abbreviations: DM, diabetes mellitus; FFA, free fatty acids; IR, insulin resistance; NASH, nonalcoholic steatohepatitis; ROS, reactive oxygen species.
Clinical and Routine Labs
- Not very Helpful

Routine Radiologic Test
(US, CT, MRI)
- Only able to detect fat
- Not Fibrosis or NASH

Liver Biopsy & Pathologic Protocols

Diagnostic & Prognostic Biomarkers for NASH

Clinical and Routine Labs
- Based on routine tests
  Fibrosis:
  - APRI, Fib-4, Simple, BARD, BAAT, Fibrotest, NAFLD Fibrosis Score
  NASH:
  - Hair, NASH test, NPI

New Modalities
- Fibroscan: Central Obesity
- MR Elastography better

New Pathogenic Biomarkers
  Fibrosis:
  - Fibrotest, ELF, Fibrometer
  NASH:
  - CK-18, NAFLD Diagnostic Panel

Diagnostic & Prognostic Biomarkers for NASH

Routine Radiologic Test
(US, CT, MRI)
- Only able to detect fat
- Not Fibrosis or NASH

Liver Biopsy & Pathologic Protocols

Clinical and Routine Labs
- Not very Helpful

New Modalities
- Fibroscan: Central Obesity
- MR Elastography better

Diagnostic & Prognostic Biomarkers for NASH

Clinical and Routine Labs
- Based on routine tests
  Fibrosis:
  - APRI, Fib-4, Simple, BARD, BAAT, Fibrotest, NAFLD Fibrosis Score
  NASH:
  - Hair, NASH test, NPI

New Pathogenic Biomarkers
  Fibrosis:
  - Fibrotest, ELF, Fibrometer
  NASH:
  - CK-18, NAFLD Diagnostic Panel
Pathogenic Pathways-based Biomarkers

- CK-18 fragments
- Circulating active caspase 3
- Fas/FasL

- Lipid Peroxidation products
- Antioxidant capacity
- Protein oxidation products

- TGF-beta, HA, Laminin, Other ECM component, Tissue Elasticity

- Tumor Necrosis Factor (TNF-alfa), Adiponectin, CRP, IL-6, CCl-2, IL1-beta, Resistin, Visfatin, RBP-4

Modified From Wieckowska A. et al. Seminars In Liver Disease/Volume 28, Number 4, 2008
Treatment of Non-alcoholic Fatty Liver Disease

NAFLD

- Insulin resistance
- Obesity
- Dyslipidemia

- Lipogenesis↑
- Lipolysis↓

- PUFAs
- PPAR δ
- PPAR α/δ
- FIBRATES
- ANTI-OXIDANTS
- UDCA and DERIVATIVES

- Oxidative stress

- MONOCLONAL ANTIBODY
- Fibrosis
- Cirrhosis

- STATINS and EZETIMIBE
- FXR AGONISTS
- ORLISTAT
- RAS BLOCKERS
- PENTOXIFYLLINE and ANTI-TNFα
Treatment of NAFLD-Old Regimens

- Lipid Lowering agents (statins, fibrates etc.)
- Anti-obesity medications
- Antioxidants
  - Vitamin E/Vitamin C
  - Betaine
  - N-Acetyl-cysteine
  - Lecithin
  - Silymarin
  - Beta-carotene
  - EPA
- Treatment of IR
- PPRA agonists
- Anti-TNF agents (Pentoxifylline)
- ACE inhibitors/ARBs
- Caspase inhibitors
- Bile Acid- Ursodeoxycholic acid (UDCA)
- Probiotics
Given the lack of evidence to show that patients with NAFLD and NASH are at increased risk for serious drug-induced liver injury from statins, **statins can be used to treat dyslipidemia in patients with NAFLD and NASH** (US Guideline: Strength – 1, Quality – B)

Until RCTs with histological endpoints prove their efficacy, **statins should not be used to specifically treat NASH** (US Guidelines: Strength – 1, Quality B)
<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Dose</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arendt</td>
<td>80</td>
<td>1000 IU/d</td>
<td>Placebo</td>
<td>Improved steatosis (assessed by CT scan) vs placebo</td>
</tr>
<tr>
<td>Sanyal</td>
<td>247</td>
<td>800 IU/d</td>
<td>Pioglitazone, placebo</td>
<td>Improved steatosis, inflammation, and ballooning vs placebo</td>
</tr>
<tr>
<td>Lavine</td>
<td>173</td>
<td>800 IU/d</td>
<td>Metformin, placebo</td>
<td>Improved steatohepatitis and ballooning vs placebo</td>
</tr>
<tr>
<td>Harrison</td>
<td>45</td>
<td>1000 IU/d</td>
<td>Placebo</td>
<td>Improved fibrosis vs baseline</td>
</tr>
</tbody>
</table>

**Vitamin E** (α-tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population. (Strength -1, Quality - B) Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis (US Guidelines: Strength - 1, Quality - C).
## PPAR-γ Agonist

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Drug</th>
<th>Time</th>
<th>DM?</th>
<th>Cirrhosis</th>
<th>ALT</th>
<th>Fat</th>
<th>Bal</th>
<th>Infl</th>
<th>Fibrosis</th>
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<tbody>
<tr>
<td>Caldwell 2001</td>
<td>10</td>
<td>Troglit 400 mg</td>
<td>3-6 months</td>
<td>1/10</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>?Yes</td>
<td>No</td>
</tr>
<tr>
<td>Promrat 2004</td>
<td>18</td>
<td>Pio 30 mg</td>
<td>12</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Aithal 2008</td>
<td>74</td>
<td>Pio 30 mg</td>
<td>12 mo</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</tr>
<tr>
<td>Belfort 2006</td>
<td>55</td>
<td>Pio 45 mg</td>
<td>6 mo</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Ratziu 2008</td>
<td>63</td>
<td>Rosi 8 mg</td>
<td>12 mo</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>---</td>
<td>---</td>
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</tr>
<tr>
<td>Sanyal 2010</td>
<td>247</td>
<td>Pio 30 mg</td>
<td>96 wk</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>---</td>
<td>Yes</td>
<td>---</td>
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<td>Mahady 2011</td>
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<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
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<td>n/a</td>
<td>n/a</td>
<td>Yes</td>
</tr>
</tbody>
</table>
**PPAR-γ Agonist: Pioglitazone**

- **PIVENS:** RCT NASH without DM (N=247)
  - Pioglitazone 30 mg/d (N=80) for 96 weeks
  - Vit E 800 IU/d (N=84) for 96 weeks
  - Placebo (N=83) for 96 weeks
  - Pre- and Post Liver Biopsy
  - Primary endpoint: NAS score decrease of 2 (no higher fib)
  - Secondary endpoints (Path features, enzymes, etc.)
- **Met primary endpoint:** Pi 34%, VE 43% & P 19%
- Histologic secondary endpoints were seen for both Pio and Vit E but no improvement in fibrosis scores
- **Conclusions:**

  *Pioglitazone* can be (?) used to treat steatohepatitis in patients with biopsy-proven NASH. However, it should be noted that majority of the patients who participated in clinical trials that investigated pioglitazone for NASH were non-diabetic and that **long term safety and efficacy** of pioglitazone in patients with NASH is not established. (US Guidelines: Strength – 1, Evidence- B)
## Treatment of NAFLD-New Regimens

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farnesoid X Receptor (FXR) Agonist</td>
<td>Obeticholic Acid (OCA)</td>
</tr>
<tr>
<td>Anti-lysyl oxidase-like 2 monoclonal antibody</td>
<td>Simtuzumab</td>
</tr>
<tr>
<td>Fatty acid/bile acid conjugate</td>
<td>Aramchol</td>
</tr>
<tr>
<td>Dual inhibitor of CCR2 and CCR5</td>
<td>Cenicriviroc</td>
</tr>
<tr>
<td>Dual peroxisome proliferator-activated receptor alpha/delta agonist</td>
<td>GFT505</td>
</tr>
<tr>
<td>Probiotics</td>
<td>VSL#3</td>
</tr>
</tbody>
</table>
Probiotics

Wong A 2013
Lepicol: 10 g/d (N=10) RCT 6 Reduced AST Reduced IHTG

Vajro P 2011
Lactobacillus GG: 12 bln CFU/d (N=10 ped) RCT 2 Decreased ALT Unchanged

Loguercio C 2002
Bio-Flora: 4/d (N=10) OL 2 Dec ALT&GGT NR

Loguercio C 2005
VSL#3: 450 bln/d (n=22) OL NR MDA and 4-HNE NR

Solga S 2008
VSL#3: 450 bil/d (N=4) OL 4 Increased liver fat Increased liver fat

Aller R 2011
Lactobacillus bulgaricus streptoc. Thermophiles: 500 million CFU/d(N=14) RCT 3 De AST and ALT NR

Malaguarna M 2011
Bifidobacterium longum and Fos: 2.5 g/d + vit B1, B2, B6, B12 + life style (N=34) RCT 4 Improved FS, HOMA, AST, LDL, CRP, TNF-α, Decreased US bright liver

Shavakhi A 2012
Proxetin: 2 tablets/d+Metformin: 500 mg/d (N=34) RCT 6 Reduced ALT Reduced US grade

Eslamparast T 2014
Proxetin 2 tabs/d (N=26) RCT 6 Reduced ALT, AST, HOMA, GGT, IC Improve

Alisi A 2014
VSL#3 RCT 4 Increased GLP-1 Improved fat

Bajaj J, Hylemon B, Younossi Z. Am J Gastroenterol 2012
Paolella G WJG 2014
Obeticholic Acid (OCA)

• Semisynthetic bile acid analog (6α-ethyl-chenodeoxycholic acid) 100 times more potent than chenodeoxycholic acid in binding farnesoid X receptor
• Treatment with OCA has been associated with
  – Improved insulin sensitivity
  – Reductions in markers of liver inflammation and fibrosis
  – Reductions in triglyceride levels
  – Dose-related weight loss
  – OCA was generally well tolerated; adverse effects were similar across treatment groups
  – Increases in LDL and reductions in HDL

**FLINT Phase 2 Trial Design**

The Farnesoid X Receptor Ligand Obeticholic Acid (OCA) in NASH Treatment (OCA vs. Placebo for 72 Weeks N=283)

<table>
<thead>
<tr>
<th></th>
<th>Total cholesterol</th>
<th>LDL</th>
<th>HDL</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OCA (mg/dL)</td>
<td>OCA (mg/dL)</td>
<td>OCA (mg/dL)</td>
<td>OCA (mg/dL)</td>
</tr>
<tr>
<td>Baseline</td>
<td>190</td>
<td>112</td>
<td>42</td>
<td>196</td>
</tr>
<tr>
<td></td>
<td>Pla (mg/dL)</td>
<td>197</td>
<td>111</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Δ Baseline - 72 wks</td>
<td>-7*</td>
<td>-8*</td>
<td>-20</td>
</tr>
<tr>
<td></td>
<td>+6*</td>
<td>+9*</td>
<td>-1*</td>
<td>+1*</td>
</tr>
<tr>
<td></td>
<td>Δ Baseline - 96 wks</td>
<td>-12</td>
<td>-12</td>
<td>-3</td>
</tr>
<tr>
<td></td>
<td>-12</td>
<td>-12</td>
<td>+1</td>
<td>0</td>
</tr>
</tbody>
</table>

Pruritus higher in OCA group (23% vs 6%) 1 dc’d OCA
Other AEs were similar to placebo and most SAE unrelated to therapy
Peroxisome Proliferator-activated Receptor (PPAR) Agonist

- **PPAR-α**: 
  - ↑ β-oxidation
  - ↓ Steatosis

- **PPAR-γ**: 
  - ↓ Steatosis
  - ↑ Insulin Sensitivity
  - ↓ Inflammation

- **PPAR-α/δ**: 
  - ↓ Hepatic Steatosis
  - ↑ Insulin Sensitivity
  - ↓ Inflammation
  - ↓ Fibrosis
  - ↓ Dyslipidemia

While no significant effect of Elafibranor was observed on resolution of NASH without worsening of fibrosis as predefined in the protocol, in the global population, significant effect of Elafibranor 120 mg was obtained with the new recommended definition.

**Resolution of NASH without worsening of fibrosis (N=274)**

- **OR (95% CI)**
  - 1.53 (0.70–2.34)
  - p=0.28
- **OR (95% CI)**
  - 2.31 (1.02–5.24)
  - p=0.045

- **Complete resolution of ballooning and either 0 or 1 for lobular inflammation**

Ratziu V, et al. AASLD 2015, San Francisco. #105
Simtuzumab—Mechanism of Action

- Humanised monoclonal antibody
- Inhibits cross-linking of collagen in pathologic stroma
- Lysyl oxidase-like 2 (LOXL2) levels may correlate with extent of fibrosis and clinically relevant endpoints for idiopathic pulmonary fibrosis
- Very limited data from early human trials

Gilead’s Phase 2b, Dose-Ranging, Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Safety and Efficacy of Simtuzumab

Treatment:
- Arm A: Simtuzumab 700 mg IV q 2 weeks for up to 240 weeks
- Arm B: Simtuzumab 200 mg IV q 2 weeks for up to 240 weeks
- Arm C: Placebo to match simtuzumab IV q 2 wks for up to 240 wks

Compensated NASH Cirrhosis Endpoints:
- Primary Outcomes:
  - Change in HVPG (Baseline to Wk 96 ]
  - Event free survival liver (related events: LT, Qualification for LT, MELD>15, EVB, Ascites, HE, ≥ 2 point increase in CPT score, new varices

GS-4997 Alone (ASK-1 Inhibitor) or in Combination With Simtuzumab—Phase II Trial

• Phase 2, Randomized, Open Label Study Evaluating the Safety, Tolerability, and Efficacy of GS-4997 Alone or in Combination With Simtuzumab in NASH and Fibrosis Stages F2-F3

• Intervention:
  • Arm A: GS-4997 6 mg QD+SIM 125 mg SQ weekly for 24 wks
  • Arm B: GS-4997 18 mg QD+SIM 125 mg SQ weekly for 24 wks
  • Arm C: SIM 125 mg SQ weekly for 24 weeks

• NASH with F2-F3

• Primary Outcomes:
  • Adverse event of GS-4997 (Treatment-emergent SAE, worsening AST & ALT)
  • Percent who prematurely discontinued drug or study due to AE

How Do We Manage our NAFLD Patients in 2016?

Elevated aminotransferases
Fatty Liver by imaging

• Exclude other causes of CLD
• Confirm lack of excessive ETOH
• Assess risk factors
• Consider Assessment for IR

No evidence of other CLD
Young age
No evidence of adv LD

Self directed life style modifications
Professionally directed life style modification
Repeat lab in 6 months

Goals achieved
Monitor q 6-12 m

Liver biopsy

Suspicion for other CLD
Dx of NAFLD uncertain

Unsuccessful
Risks (DM, IR)
Liver enzymes elevated
High NAFLD Fibrosis score

Transient Elastography
### How Do We Manage our NAFLD Patients in 2016?

**Assessment for NASH or Fibrosis**

- **Histologic NASH or Evidence of Fibrosis**
  - Continue life style and modifications
  - If non-diabetic: VIT E
  - If diabetic: Pioglitazone?

- **Steatosis no evidence of significant fibrosis**
  - Refer to primary for management of MS and risk of CVD

- **Medical treatment unsuccessful**
  - Consider RCT of new agents
  - Consider Bariatric surgery for those who meet criteria

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**ICVH 2016**

**INTERNATIONAL CONFERENCE ON VIRAL HEPATITIS**
Non-Alcoholic Steatohepatitis: What Is It and How Do We Treat and Monitor?

- NAFLD has tremendous clinical, economic and QoL burden to the patients and to the society and this burden is growing globally
- NASH is the progressive form of NAFLD
- Histologic fibrosis (stage 2 or more) predicts LRM
- Pathogenesis of NASH is complex (multiple hits)
- Biomarkers should be based on pathogenic pathways
- Current treatment for patients with NASH:
  - Life style modifications for all
  - Vitamin E for non-DM NASH
  - ??Pio for DM with NASH but be aware of safety concerns
  - Consider bariatric surgery for morbidly obese+/-DM with NASH
- Future treatment considerations:
  - Clinical trials of new agents are underway