NASH Management: Agents in Late Stage Development

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**Consultant:** Salix, Clinical Area- HE, IBS-D

**Speakers Bureau:** AbbVie, Clinical Area- HCV

**Speakers Bureau:** Salix, Clinical Area- HE, IBS-D

**Speakers Bureau:** Intercept, Clinical Area- PBC
Learning Objectives

• Upon completion of this activity, participants should be able to:
  – Understand the current available treatment for NAFLD/NASH
  – Describe the mechanisms of action of novel agents in study for future treatment of NASH
  – Discuss recent evidence regarding the safety and efficacy of new and emerging agents for the treatment of NASH
Current Treatment for NAFLD/NASH
Goals of NASH Treatment

- Improve metabolic abnormalities
- Decrease inflammation
- Prevent/arrest/reverse liver fibrosis
  - AASLD recommends pharmacological treatments aimed primarily at improving liver disease should generally be limited to those with biopsy-proven NASH and fibrosis
- Prevent advanced liver disease, liver failure, liver cancer and related outcomes
- Systemic outcomes (eventually)

Lifestyle Recommendations for Treating NASH

**Caloric intake reduction**
≥30% or ~750-1,000 kcal/day
Improved insulin resistance and hepatic steatosis
*Limit consumption of fructose-enriched beverages

**Weight loss**
3% to 5% can improve steatosis, but 6% to 10% is needed to improve NASH/fibrosis

**Exercise**
Alone may reduce steatosis, but effect on other histologic features unknown

**No heavy alcohol consumption**
Insufficient data to guide recommendations regarding nonheavy alcohol consumption
**Drink ≥2 cups of caffeinated coffee daily**

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*Fructose increases the odds of the development of nonalcoholic fatty liver in high-risk patients and of nonalcoholic steatohepatitis and more advanced liver fibrosis in patients who already have nonalcoholic fatty liver disease.

Vitamin E (800 IU/day)
- May be considered for non-diabetic adults with biopsy-proven NASH (counsel patients on risks and benefits)
  - Improves liver histology, but not fibrosis
  - Long-term safety issues concerns linger (eg, impact on long-term mortality, prostate cancer)
- Vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis
  - More data on safety and efficacy are needed

• Improves liver histology in patients with and without T2DM and biopsy-proven NASH
  – May be used in treatment
• Should not be used in NAFLD without biopsy-proven NASH
• 2.5 to 4.7-kg weight increase in body weight with 12- to 36-month treatment
• Recent meta-analysis refutes concern about bladder cancer
• Bone loss may occur

Primary Outcome

- **Vitamin E 800 IU/d (n=84)**
- **Pioglitazone 30 mg/d (n=80)**
- **Placebo (n=83)**

- **Patients, %**
  - 0
  - 20
  - 40
  - 60
  - 80
  - 100

- **P=0.001**
- **P=0.04**
- **P=0.04**

*Defined as NAS improvement by >2 points, including >1-point improvement in ballooning + 1-point improvement in either lobular inflammation or steatosis score + no increase in fibrosis.*

Pioglitazone for NASH in Patients With Prediabetes or T2DM

Key Outcomes at 18 Months

- **Primary Outcome**: Reduction of ≥2 points in the NAFLD Activity Score in 2 histologic categories without worsening of fibrosis

  - **Pioglitazone 45 mg/d (n=50)**: 58 patients, **P<0.01**
  - **Placebo (n=51)**: 17 patients

- **NASH resolution**

  - **Pioglitazone 45 mg/d (n=50)**: 51 patients, **P<0.01**
  - **Placebo (n=51)**: 19 patients

Metabolic and histologic improvement continued over 36 months

Patients with NAFLD are at high risk for cardiovascular morbidity and mortality
- Aggressive modification of CVD risk factors should be considered in all patients with NAFLD
Statins can be used to treat dyslipidemia in patients with NAFLD and NASH
- Statins may be used in patients with NASH cirrhosis, but should be avoided in patients with decompensated cirrhosis

## Treatments Not Currently Recommended for NASH

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>• Does not improve liver histology despite reducing ALT and insulin resistance</td>
</tr>
</tbody>
</table>
| GLP-1 agonists   | • Trial of liraglutide showed resolution of NASH, less fibrosis progression, weight loss  
                  | • Further trials expected                                                   |
| UDCA             | • Histologic benefit not shown                                            |
| Omega-3 fatty acids | • No proven benefit in NASH  
                      | • Can be used for hypertriglyceridemia                                    |
| Obeticholic acid | • Phase 3 trials at higher dose than for PBC                              |
| Probiotics       |                                                                           |

Summary: Current Treatments for NASH

Assessment for NASH or evidence of significant fibrosis

- Histologic NASH or evidence of significant fibrosis

- Lifestyle modification
  - Weight loss 7% to 10%; preferably >10%
  - Refrain from consuming alcohol
- Vitamin E 800 IU/d if not diabetic
- Pioglitazone
- Statins for dyslipidemia
- Consider bariatric surgery for those who meet criteria

Steatosis, but no evidence of significant fibrosis

Management of metabolic syndrome and CVD risk

Emerging Treatment Options for NAFLD/NASH
NASH Clinical Trial Endpoints in Early Phase III Development: Liver Histologic Improvement

**NASH Resolution**
- Resolution of steatohepatitis on overall histopathologic reading
- No worsening of liver fibrosis

**Fibrosis Improvement**
- Improvement $\geq 1$ fibrosis stage
- No worsening of steatohepatitis

NASH Clinical Trial Endpoints in Early Phase II Development

ALT

10 U/L reduction associated with histologic improvement or resolution of NASH\(^1\)

\( \geq 17 \) U/L reduction predicts histologic response\(^2\)

Liver Fat Fraction (MRI-PDFF)

\( \geq 5\% \) absolute reduction associated with improvement in steatosis\(^3\)

\( \geq 30\% \) relative reduction associated with improvement in NAFLD activity score without fibrosis worsening\(^4\)

- In large clinical trials that include paired biopsies, surrogate endpoints can be validated against histologic endpoints

Slide credit: [clinicaloptions.com](http://clinicaloptions.com).

Gut-Liver Axis/Bile Acids
Mechanisms of Late-Stage Investigational Agents for NASH: Obeticholic Acid

Insulin resistance
↑ insulin/glucose

Lipogenesis
↑ FFA

ER stress

Mitochondrial dysfunction

Apoptosis
↑ TGF-β
↑ TGF-α
↑ IL-6

Collagen deposition

VLDL
↓

SHP
↑

FFA
↑

Obeticholic acid
FXR agonist

Bile acids

ASK1, apoptosis signal-regulating kinase; TRAF1, tumor necrosis factor receptor factor 1.
The REGENERATE Study

2065 patients with biopsy-confirmed NASH; F1–3

Screen* 0 18 48 EOS

Interim analysis 1 Interim analysis 2

Accrual of pre-specified number of events†

*NASH confirmed by biopsy ≤6 months before Day 1. †Placebo and OCA 25-mg groups only.

Abbreviations: EOS, end of study; OCA, obeticholic acid.

Obeticholic Acid*: The REGENERATE Study

• “In the primary efficacy analysis, once-daily OCA 25 mg met the primary endpoint of fibrosis improvement (≥1 stage) with no worsening of NASH at the planned 18-month interim analysis (p=0.0002 vs. placebo)”

• Phase 3 study in NASH patients with stage 2 and 3 fibrosis

<table>
<thead>
<tr>
<th>Fibrosis improvement at Month 18</th>
<th>Placebo</th>
<th>OCA 10 mg</th>
<th>OCA 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT Population: NASH with stage 2 or 3 Fibrosis</td>
<td>N= 311</td>
<td>N= 312</td>
<td>N= 308</td>
</tr>
<tr>
<td>Fibrosis Improvement (≥1 stage) with no worsening of NASH</td>
<td>11.9%</td>
<td>17.6% (p=0.0446)</td>
<td>23.1% (p=0.0002)</td>
</tr>
<tr>
<td>Fibrosis Improvement &gt;2 stages with no worsening of NASH</td>
<td>4.5</td>
<td>7.1</td>
<td>13.3</td>
</tr>
<tr>
<td>NASH resolution without worsening of fibrosis</td>
<td>8</td>
<td>11.2</td>
<td>11.7</td>
</tr>
</tbody>
</table>

* Under FDA review
### Primary efficacy endpoints (ITT patients with stage 2,3 fibrosis)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=311)</th>
<th>OCA 10 mg (n=312)</th>
<th>OCA 25 mg (n=308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis improvement ≥ 1 stage with no worsening of NASH*</td>
<td>11.9%</td>
<td>17.6% (p=0.0446)</td>
<td>23.1% (p=0.0002)</td>
</tr>
<tr>
<td>NASH resolution with no worsening of fibrosis</td>
<td>8.0%</td>
<td>11.2% (p=0.1814)</td>
<td>11.7% (p=0.1268)</td>
</tr>
</tbody>
</table>

### Additional full efficacy (ITT patients + patients with stage 1 fibrosis at risk for progression)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=407)</th>
<th>OCA 10 mg (n=407)</th>
<th>OCA 25 mg (n=404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis improvement ≥ 1 stage with no worsening of NASH*</td>
<td>10.6%</td>
<td>15.7% (p=0.0286)</td>
<td>21.0% (p&lt;0.0001)</td>
</tr>
<tr>
<td>NASH resolution with no worsening of fibrosis</td>
<td>7.9%</td>
<td>11.3% (p=0.0903)</td>
<td>14.9% (p=0.0013)</td>
</tr>
</tbody>
</table>

*Defined as no worsening of hepatocellular ballooning, no worsening of lobular inflammation and no worsening of steatosis.
The REGENERATE Study: Safety

- The frequency of serious AEs was similar across treatment groups (11–14%)
- No single serious adverse event occurred in more than 1% of patients in any treatment group
- The most frequent adverse event was pruritus

<table>
<thead>
<tr>
<th>Treatment-emergent and serious adverse events</th>
<th>Placebo (n = 657)</th>
<th>Obeticholic acid 10 mg (n = 653)</th>
<th>Obeticholic acid 25 mg (n = 658)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one treatment-emergent adverse event</td>
<td>548 (83%)</td>
<td>579 (89%)</td>
<td>601 (91%)</td>
</tr>
<tr>
<td>Severity*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>160 (24%)</td>
<td>163 (25%)</td>
<td>130 (20%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>294 (45%)</td>
<td>323 (49%)</td>
<td>338 (51%)</td>
</tr>
<tr>
<td>Severe</td>
<td>87 (13%)</td>
<td>89 (14%)</td>
<td>130 (20%)</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>5 (1%)</td>
<td>4 (1%)</td>
<td>2 (&lt; 1%)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (&lt; 1%)</td>
<td>0</td>
<td>1 (&lt; 1%)</td>
</tr>
<tr>
<td>Leading to treatment discontinuation</td>
<td>41 (6%)</td>
<td>39 (6%)</td>
<td>83 (13%)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>75 (11%)</td>
<td>72 (11%)</td>
<td>93 (14%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events in ≥ 5% of patients in either obeticholic acid group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Grade 1 (mild of localized)</td>
</tr>
<tr>
<td>Grade 2 (intense or widespread)</td>
</tr>
<tr>
<td>Grade 3 (Intense or widespread and limit activities of daily living)</td>
</tr>
</tbody>
</table>
Inflammation/Fibrosis Targets
Mechanisms of Late-Stage Investigational Agents for NASH: Liraglutide

Liraglutide
GLP-1 agonist

↓ VLDL
↑ SHP
↑ FXR/TGR5
Bile acids

Insulin resistance
↑ insulin/glucose

Mitochondrial dysfunction

Collagen deposition

Lipogenesis
↑ FFA
ER stress

Apoptosis

HSC activation

↑ TGF-β
↑ TGF-α
↑ IL-6
Kupffer cell

ASK1, apoptosis signal-regulating kinase; TRAF1, tumor necrosis factor receptor factor 1.
Multifactorial Effects of GLP1RA

WEIGHT LOSS

- Increases satiety
- Delays gastric emptying

GLYCEMIC CONTROL

- Insulin secretion
- Glucagon secretion

GLYCAEMIC CONTROL

CV BENEFITS

- Improves lipid profile
- Reduces systemic inflammation
- Reduces Blood pressure

LIPOGENESIS

IMPROVEMENT IN NASH?
### Outcomes at 48 Weeks

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Liraglutide 1.8 mg/day (n=23)</th>
<th>Placebo (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution of NASH</td>
<td>39</td>
<td>9</td>
</tr>
<tr>
<td>Improved ballooning</td>
<td>61</td>
<td>32</td>
</tr>
<tr>
<td>Improved inflammation</td>
<td>48</td>
<td>55</td>
</tr>
<tr>
<td>Improved fibrosis</td>
<td>26</td>
<td>14</td>
</tr>
<tr>
<td>Worsened fibrosis</td>
<td>9</td>
<td>36</td>
</tr>
</tbody>
</table>

## Safety of Liraglutide in Patients With Diabetes

<table>
<thead>
<tr>
<th>Event</th>
<th>Liraglutide 1.2 mg n= 645</th>
<th>Liraglutide 1.8 mg n= 1024</th>
<th>Placebo n= 661</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>18</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Back pain</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

*Adverse Reactions Reported in ≥5%*\(^a\) of Liraglutide-treated Patients with Diabetes

\(a\)Excluding hypoglycemia.

Liraglutide (Victoza) [prescribing information]. Plainsboro, NJ; Novo Nordisk, Inc.; 2017.
Metabolic Targets
Mechanisms of Late-Stage Investigational Agents for NASH: Resmetirom

- T4 prohormone
- T3, active hormone
- TSH, thyroid stimulating hormone

↓ VLDL
↑ SHP
↑ FXR/TGR5
Bile acids

↑ insulin/glucose

↑ Lipogenesis
↑ FFA

ER stress

Collagen deposition

Mitochondrial dysfunction

Apoptosis

↑ TGF-β
↑ TGF-α
↑ IL-6

HSC activation

Resmetirom
THR-beta agonist

Kupffer cell

ASK1, apoptosis signal-regulating kinase; TRAF1, tumor necrosis factor receptor factor 1.
Resmetirom: Wk 12 Efficacy for Treatment of NASH (ITT Population)

- Randomized, double-blind, placebo-controlled phase II trial in patients with biopsy-confirmed NASH with hepatic fat fraction ≥ 10%

**Primary Endpoint:**
Relative Change in Hepatic Fat Fraction Assessed by MRI-PDFF

<table>
<thead>
<tr>
<th></th>
<th>Resmetirom</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Change From Baseline (%)</td>
<td>-32.9%</td>
<td>-10.4%</td>
</tr>
</tbody>
</table>

Least squares mean difference from baseline (95% CI): -22.5% (-32.9 to -12.2), *P* < .0001
Resimetrom Significantly Decreases Hepatic Fat in NASH Patients at Week 12 MRI-PDFF, and Was Associated With NASH Resolution at Week 36 Biopsy

## Safety of Resmetirom

<table>
<thead>
<tr>
<th>Patients with AE's n (%)</th>
<th>Main study (36wk)</th>
<th>Extension (36wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=42</td>
<td>Resmetirom N=31</td>
</tr>
<tr>
<td>Severe</td>
<td>28 (68)</td>
<td>18 (58)</td>
</tr>
<tr>
<td>Moderate</td>
<td>13 (32)</td>
<td>10 (32)</td>
</tr>
<tr>
<td>Mild</td>
<td>13 (32)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Patient with SAE's</td>
<td>2 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

### Most common AE's n (%)

<table>
<thead>
<tr>
<th>AE</th>
<th>Main study (36wk)</th>
<th>Extension (36wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>4 (10)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (5)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (15)</td>
<td>0</td>
</tr>
<tr>
<td>UTI</td>
<td>4 (10)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (10)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

### Grade 3 CTC

<table>
<thead>
<tr>
<th>CTC</th>
<th>Main study (36wk)</th>
<th>Extension (36wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT&gt;5xULN</td>
<td>3 (7)</td>
<td></td>
</tr>
<tr>
<td>GGT&gt;5xULN</td>
<td>5 (12)</td>
<td>0</td>
</tr>
</tbody>
</table>

Harrison Stephen, et al. “EFFECTS OF RESMETIROM (MGL3196) ON HEPATIC FAT, LIPIDS, LIVER ENZYMES AND MARKERS OF LIVER FIBROSIS IN AN OPEN LABEL 36 WEEK EXTENSION STUDY IN NASH PATIENTS”.  
https://www.madrigalpharma.com/newsroom/nash-experts-webcasts/
Conclusions

- Patients with histologic NASH or evidence of significant fibrosis should be treated according to AASLD guidelines.

- Many potential mechanisms in NASH represent disease-specific therapeutic targets.
  - Multiple trials targeting a wide array of potential NASH pathogenic pathways are underway.
  - Combination therapies with different targets may provide a synergistic histopathologic benefit.

- Combination therapy using drugs with different mechanisms of action is likely the future of NASH treatment.