Primary Biliary Cholangitis (PBC)
  – Accepted surrogates for disease
  – Efficacy of current therapy
  – New treatments for incomplete or UDCA null responders

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH):
  – Defining the disease and patient selection for treatment
  – Current approach to therapy
  – Emerging therapy
Primary Biliary cholangitis (PBC)

Stage 1: Portal Inflammation
Florid Duct Lesion

Stage 2: Duct Proliferation
Periportal Hepatitis

Stage 3: Cholestasis
Bridging Fibrosis

Stage 4: Cirrhosis


PBC Epidemiology

- 90-95% Women
- Predominantly Caucasians
- 3-15 cases / 1,000,000 per year
- Age Range of Diagnosis: 30-65 years (~90%)

**PBC: Pathogenesis**

- Chronic, progressive autoimmune cholestatic liver disease
  - Circulating autoantibodies (+AMA)
  - Associated autoimmune diseases
  - Impaired T suppressor cell function
  - ANA/ASMA + in ≈30%

- Genetic factors
  - RR in first-degree relatives: 50-100X higher than general population

- Environmental factors


**PBC Signs and symptoms**

- ↑Alkaline phosphatase
- ↑GGT

- Asymptomatic (48 – 60%)
- Symptomatic
  - Fatigue (70%)
  - Pruritus (55%)
  - Jaundice (16%)
  - Bleeding (3%)
  - Weight loss

Most patients with PBC have elevated total cholesterol (>200 mg/dL)
- 75% of asymptomatic patients
- 96% of symptomatic patients

Largely caused by presence of lipoprotein X (LpX)
- Abnormal LDL particle derived from biliary lipids that spill into the blood
- Rich in free cholesterol and phospholipids
- LpX is not taken up into atherosclerotic plaques
- Has anti-atherogenic properties

HDL often high

PBC associated hyperlipidemia

PBC natural history

Asymptomatic | Symptomatic | w/ Jaundice | Liver Failure
---|---|---|---
1 - 20 yrs | 10-12 yrs | 5-7 yrs

Rate of Disease Progression (Highly Variable)

Age
Bilirubin
Histology
Albumin

Lindor KD, *Hepatology* 1996
UDCA Major Trials Summary

<table>
<thead>
<tr>
<th>Study</th>
<th># Patients</th>
<th>UDCA Dose (mg/kg/d)</th>
<th>Clinical Parameters (Significant Improvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poupon 1994</td>
<td>146</td>
<td>13 – 15</td>
<td><img src="none" alt="●" /> <img src="none" alt="●" /> <img src="none" alt="●" /> <img src="none" alt="●" /></td>
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<tr>
<td>Heathcote 1994</td>
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<td>14</td>
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<tr>
<td>Lindor 1994 (96)</td>
<td>180</td>
<td>13 – 15</td>
<td><img src="none" alt="●" /> <img src="none" alt="●" /> <img src="none" alt="●" /></td>
</tr>
</tbody>
</table>

*Survival free from Transplant

URSO Mechanism of Action

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophilic, non-cytotoxic Bile Acid</td>
<td></td>
</tr>
<tr>
<td>Reduces intracellular hydrophobic bile Acids</td>
<td>Cytoprotective</td>
</tr>
<tr>
<td>Decreases damage to biliary epithelium</td>
<td></td>
</tr>
<tr>
<td>Enhances Bile Acid secretion MRP2 Apoptosis</td>
<td>Choleretic</td>
</tr>
</tbody>
</table>

ALP values have predictive significance in addition to bilirubin values

- Normal Bilirubin
- Abnormal Bilirubin
- ALP ≤1.67xULN
- ALP >1.67xULN

15 year Survival (%)

---

Reported Incidence of UDCA Treatment Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Failure (%)</th>
</tr>
</thead>
</table>
| Pells et al, 2013¹ (UK-PBC group) | • 60% of patients presenting at age <40 years  
• 10% of patients presenting at age >70 years |
| Corpechot et al, 2011²        | 13%–37%*                                                   |
| Kuiper et al, 2009³           | 34%–38%*                                                   |
| Corpechot et al, 2008⁴        | 35%–39%*                                                   |

*Depending on criteria used. Abbreviation: UDCA, ursodeoxycholic acid.

**Approach to incomplete or non-response to UDCA?**

- No clear, proven choices
- Query patient for adherence
  - Barriers to adherence: weight gain, loose stools, hair loss
- Confirm UDCA dosage 13–15 mg/kg
  - Doubling UDCA dose has not shown benefit
- Check for co-morbid liver disease
- Consider co-administration of bile acid sequestrant
- Refer patient to clinical trial
  - Many promising drugs being investigated

**Abbreviation:** UDCA, ursodeoxycholic acid.


**Drugs Under Evaluation for PBC**

- Rituximab (B-cell depletion)
- Fibrates (PPAR-α agonists)
- Nor-ursodeoxycholic acid (bicarbonate “umbrella,” anti-inflammatory, antifibrotic)
- Obeticholic acid (6-ethyl chenodeoxycholic acid, FXR agonist)
- FGF19 analogs

**Abbreviations:** FGF19, fibroblast growth factor 19; FXR, farnesoid X receptor; PBC, primary biliary cirrhosis; PPAR, peroxisome proliferator-activated receptor.
Rituximab for PBC with incomplete response to UDCA

Tsuda M, et al. ¹
• Open-label study of rituximab in patients with PBC and incomplete responses to UDCA (n = 6)
• Well tolerated
• Reduced IgA, IgM and AMA
• Significant reductions in serum ALP levels up to 36 weeks following rituximab treatment

Myers RP, et al. ²
• Open-label study of rituximab in patients with PBC and incomplete responses to UDCA (n = 14)
• Rituximab was well tolerated and associated with reductions in serum IgM and AMA
• Limited biochemical efficacy in PBC patients with incomplete response to UDCA

Abbreviations: ALP, alkaline phosphatase; AMA, antimitochondrial antibodies; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.

Fenofibrate improves liver chemistries in PBC

• Peroxisome proliferator-activated receptor (PPAR)-α agonist
  – Regulation of bile acid synthesis and detoxification
  – Modulates phospholipid secretion
• Open-label study: Efficacy and safety of fenofibrate in patients with PBC and incomplete response to UDCA (n = 20)
  – ALP levels decreased significantly; rebound in ALP levels occurred following fenofibrate discontinuation
  – Contraindicated in patients with active liver disease or severe renal dysfunction, including PBC
• Prospective RCT
  – No effect on histology or survival *

Abbreviations: ALP, alkaline phosphatase; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.
FXR as a target to treat PBC

Abbreviations: BSEP, bile salt export pump; FXR, farnesoid X receptor; MRP 2/3/4, multidrug resistant protein 2/3/4; NTCP, sodium/taurocholate cotransporting polypeptide; OATP, organic anion transporting polypeptide; OST \( \alpha/\beta \), organic soluble transporter \( \alpha/\beta \).


FXR Ligands

Abbreviations: CDCA, chenodeoxycholic acid; FXR, farnesoid X receptor.


### Inclusion
- Definite or probable PBC diagnosis (EASL and AASLD guidelines)
- ALP $\geq 1.67 \times ULN$ and/or total bilirubin $>ULN$ to $<2 \times ULN$
- Taking UDCA for $\geq 12$ months (stable dose $\geq 3$ months) or unable to tolerate UDCA

### Exclusion
- History or presence of concomitant liver diseases
- Clinical complications of PBC or significant hepatic decompensation
- Severe pruritus requiring current or prior systemic treatment

*Titration OCA group:* 5 mg OCA for 6 months $\rightarrow$ 10 mg OCA if well tolerated and ALP $>1.67 \times ULN$ or bilirubin $>ULN$.

Abbreviations: ALP, alkaline phosphatase; ITT, intention-to-treat; OCA, obeticholic acid; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Primary Endpoint:
- ALP <1.67 x ULN
- ALP ≥15% decrease
- Bilirubin normal range

Efficacy and safety of OCA
- Consistent across patient subgroups³
- Age at diagnosis
- Disease duration
- Baseline alkaline phosphatase levels

*Comparable efficacy between titration and 10 mg groups with lower overall incidence of pruritus in titration group


OCA—Phase III POISE Trial: Change in direct bilirubin

Abbreviations: LS, least squares; OCA, obeticholic acid; SE, standard error.
Courtesy of Kris Kowdley
POISE—Lipid Changes with OCA

N = 216

**Titration OCA group:** 5 mg OCA for 6 months →10 mg OCA if well tolerated and ALP >1.67 x ULN or bilirubin >ULN

**Abbreviations:** HDL, high-density lipoprotein; LDL, low-density lipoprotein; OCA, obeticholic acid; VLDL, very low-density lipoprotein.


---

**POISE—OCA Adverse effects**

- Most common and dose-related AE
- Few patients withdrew due to pruritus (<6%)
- Cholestyramine use:
  - 11% (placebo);
  - 19% (5 → 10 mg);
  - 26% (10 mg)
- More pruritus in 10 mg vs placebo

**Abbreviations:** ALP, alkaline phosphatase; ULN, upper limit of normal.


NAFLD and NASH: Where we are and what’s on the horizon

NAFLD

- Isolated steatosis: ~70-75%
  - None to very minimal progression to fibrosis
  - No increased risk of death compared with the general population

Steatosis with mild inflammation

- Possible sampling variability with poorly defined risk of progression

~4%

NASH

- ~20-25%
  - Increased risk of death compared with general population
    - Cardiovascular
    - Malignancy
    - Liver-related

Possible fibrosis:

- Risk factors for progression:
  1. Diabetes/insulin resistance
  2. Hypertension
  3. Weight gain >5kg
  4. Rising ALT, AST, AST:ALT >1

~20%

Increased risk of death compared with general population

- Cardiovascular
- Malignancy
- Liver-related
Mortality of NAFLD

10 yr follow-up
Observed - 77%
Expected - 87%
p < 0.005

Malignancy – 28%
Ischemic heart disease – 25%
Liver disease – 13%

Adams et al., Gastroenterology 2005

Mortality due to NASH and not isolated hepatic steatosis

Isolated hepatic steatosis

NASH

Ekstedt et al., Hepatology 2006
Outcomes are associated with the presence and extent of fibrosis

Risk factors for progression
- Age
- Obesity
- DM

HCC Risk

CVD Risk

Predictability

Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus; HCC, hepatocellular carcinoma.

Angulo et al. AASLD 2014, Ekstedt 2014

NAFLD: Needs in the field

- Non-invasive diagnosis of NASH
- Non-invasive diagnosis of fibrosis
- Accurate patient phenotyping
- NASH resolution
- Effective reduction in liver fibrosis
- Improvement of portal HTN in NASH cirrhosis
- Reversal of cirrhosis
- Measures for non-invasive determination of treatment response

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; OCA, obeticholic acid; UDCA, ursodesoxycholic acid; ULN, upper limit of normal.

## Available non-invasive imaging diagnostics

<table>
<thead>
<tr>
<th>Modality</th>
<th>Technique</th>
<th>Fat quantification</th>
<th>Diagnosis of NASH</th>
<th>Early Fibrosis</th>
<th>Advanced fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>standard</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elastography</td>
<td>US/ARFI</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fibroscan</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fibroscan+C AP</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>MRE</td>
<td></td>
<td>? ✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PDFF</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-D</td>
<td>? ✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Available treatment that promotes NASH resolution


• Prospective study 293 patients with histologically proven NASH who were encouraged to adopt recommended lifestyle changes to reduce their weight over 52 weeks
• 261 had paired biopsies
• 88 (30%) lost >5% body weight
**Weight loss stabilizes or reduces fibrosis**

Vilar-Gomez et al. Gastroenterology 2015

---

**Lifestyle change**

- Foundation of any treatment plan
- Difficult to achieve and **sustain**
- Not enough for morbidly obese patients
Bariatric population

- 91% (85-98%) Fatty liver
- 37% (24-98%) NASH
- 1.7% (1-7%) Cirrhosis

\(^1\)Machado, *J Hepatol*, 2006

Indications for bariatric surgery

- Normal Weight (BMI 18.5 to 24.9)
- Overweight (BMI 25 to 29.9)
- Obese (BMI 30 to 34.9)
- Severely Obese (BMI 35 to 39.9)
- Morbidly Obese (BMI > 40)
- Super Obese (BMI > 50)

BMI = weight (kg) / height (m)\(^2\)

Candidates for obesity surgery

With co-morbidities:
- DM
- HTN
- Joint disease
- **Not liver disease**

\(^*\)2016 ACG/LGS Regional Postgraduate Course
\(^*\)Copyright 2016 American College of Gastroenterology
Bariatric surgery decreases mortality

**Table 1. Comparison of Data from Two Studies on Mortality Associated with Bariatric Surgery.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sjöström et al.</th>
<th>Adams et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery Group</td>
<td>Control Group</td>
</tr>
<tr>
<td>Mean follow-up (yr)</td>
<td>10.9</td>
<td>7.3</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>2010</td>
<td>2037</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>46.1</td>
<td>47.4</td>
</tr>
<tr>
<td>Mean body-mass index</td>
<td>41.8</td>
<td>40.9</td>
</tr>
</tbody>
</table>

**Deaths**

<table>
<thead>
<tr>
<th></th>
<th>Total no.</th>
<th>Early occurrence (%) †</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>101</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>129</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>213</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>321</td>
<td>0.52</td>
</tr>
</tbody>
</table>

- Data are from Sjöström et al. (a prospective, controlled study) and Adams et al. (a retrospective, matched-cohort study).
- † In the study by Sjöström et al., early death was defined as occurring within the first 90 days after surgery. In the study by Adams et al., the period was 3 years.

1 Bray, NEJM 2007; 2 Sjostrom et al. NEJM 2007

---

Metabolic disease after surgery

- Resolution/improvement of
  - Diabetes
  - Metabolic Syndrome
  - Hypertension
- Decreased adipose tissue lipolysis
- Decreased endogenous glucose production

Obesity Surgery – Is the Cure for NASH in the OR?

<table>
<thead>
<tr>
<th>Study</th>
<th>Surgery</th>
<th>N Total/NASH</th>
<th>N Citrullinemia</th>
<th>Mean interval to 2nd biopsy (months)</th>
<th>Mean weight loss</th>
<th>Statistics</th>
<th>Refluxing</th>
<th>Inflammation</th>
<th>Fibrosis</th>
<th>NASH resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixon, 2004</td>
<td>AGB</td>
<td>36/23</td>
<td>1</td>
<td>47 (±13.6)</td>
<td>25.6</td>
<td>52%</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>82%</td>
</tr>
<tr>
<td>Dixon, 2006</td>
<td>RYGB</td>
<td>60/30</td>
<td>45.9 (±15.4)</td>
<td>29.5</td>
<td>52%</td>
<td>↓</td>
<td>↓</td>
<td>Not reported</td>
<td>↓</td>
<td>Not reported</td>
</tr>
<tr>
<td>Muttai, 2005</td>
<td>AGB</td>
<td>78</td>
<td>2</td>
<td>54 (±11)</td>
<td>15</td>
<td>59%</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Not reported</td>
</tr>
<tr>
<td>Malhas, 2006</td>
<td>BIB</td>
<td>121/24</td>
<td>40 (±10)</td>
<td>12</td>
<td>19%</td>
<td>↓</td>
<td>Not reported</td>
<td>Not reported</td>
<td>↑</td>
<td>70%</td>
</tr>
<tr>
<td>Keil, 2004</td>
<td>BPD</td>
<td>110</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>70%</td>
</tr>
<tr>
<td>Martin, 2005</td>
<td>RYGB</td>
<td>98</td>
<td>46.7 (±6.0)</td>
<td>12</td>
<td>31.8</td>
<td>↓</td>
<td>reported</td>
<td>Not reported</td>
<td>↓</td>
<td>80%</td>
</tr>
<tr>
<td>Clark, 2005</td>
<td>RYGB</td>
<td>45</td>
<td>51.1 (±6.1)</td>
<td>10</td>
<td>35.4</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Not reported</td>
</tr>
<tr>
<td>Czernik, 2006</td>
<td>RYGB</td>
<td>14</td>
<td>44.3</td>
<td>17.5</td>
<td>72%</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>100%</td>
</tr>
<tr>
<td>de Almeida, 2006</td>
<td>RYGB</td>
<td>14</td>
<td>53.4 (±8.8)</td>
<td>23.5</td>
<td>42%</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>80%</td>
</tr>
<tr>
<td>Baker, 2006</td>
<td>RYGB</td>
<td>19/19</td>
<td>41 (±4.4)</td>
<td>21.4</td>
<td>52.4</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>100%</td>
</tr>
<tr>
<td>Liu, 2007</td>
<td>RYGB</td>
<td>39/23</td>
<td>47.7 (±6.2)</td>
<td>18</td>
<td>Not reported</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>100%</td>
</tr>
<tr>
<td>Ferron, 2007</td>
<td>RYGB</td>
<td>18/12</td>
<td>51.7 (±7.4)</td>
<td>24</td>
<td>60%</td>
<td>↓</td>
<td>Not reported</td>
<td>Not reported</td>
<td>↓</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

GLP-1, Resistin; RYGB, RYGB; PYY, peptide YY; FXR, farnesoid X receptor; NASH, non-alcoholic steatohepatitis.

Potential effects of RYGB on NASH

- ↑ Adiponectin
- ↓ Insulin resistance
- ↓ Energy intake
- Altered gut hormones
  - ↑ PYY
  - ↓ Ghrelin: ↑ appetite
  - FXR activation in the gut
  - Modification of gut flora
- ↑ Hepatic inflammation
- ↑ Hepatic steatosis
- ↑ Insulin resistance
- ↑ Glucose output
There are no FDA-approved therapies for NASH.

Compounds farthest along in development:
- Vitamin E
- TZDs
- Pentoxyfilline
- Obeticholic Acid (OCA)

Abbreviations: FDA, US Food and Drug Administration; NASH, nonalcoholic steatohepatitis; TZD, thiazolidinedione.

**Efficacy of Vitamin E**

<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>
<tr>
<td>Sanyal</td>
<td>20</td>
<td>400 IU/d</td>
<td>Vitamin E + pioglitazone</td>
<td>Improved steatosis vs baseline</td>
</tr>
<tr>
<td>Dufour</td>
<td>48</td>
<td>800 IU/d</td>
<td>UDCA + placebo, placebo</td>
<td>Improved steatosis, inflammation, and ballooning vs baseline</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; UDCA, ursodeoxycholic acid.
Why Not Empirically Treat Suspected NASH with Vitamin E?

- 50% of patients do not respond to vitamin E:
  - Liver enzymes are not reliable to assess quiescence or progression
- ↑ risk of hemorrhagic stroke
- Prostate cancer risk? (Absolute increase 1.6 per 1000 person years; synthetic form)
- Long-term safety remains unknown though likely safe
  - Increased mortality not substantiated

Abbreviation: NASH, nonalcoholic steatohepatitis.

Vitamin E and Pioglitazone both resolved NASH

![Graph showing the proportion of subjects in different study groups](chart.png)

- Vitamin E: 44/84, P <0.0008
- Placebo: 23/83, P <0.01
- Pioglitazone: 40/80

*Courtesy of AJS*
### Pioglitazone for NASH

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve$^2$</td>
<td></td>
</tr>
<tr>
<td>- Insulin sensitivity</td>
<td>- Weight gain (2−4.7 kg)</td>
</tr>
<tr>
<td>- ALT</td>
<td>- Cardiac toxicity$^1$</td>
</tr>
<tr>
<td>- Steatosis</td>
<td>- Fracture risk$^2$</td>
</tr>
<tr>
<td>- Inflammation</td>
<td>- ? Bladder cancer$^1,4$</td>
</tr>
</tbody>
</table>

Meta-analysis of 19 trials (16,390 patients) with T2DM, pioglitazone$^1$
- Death, MI, or CVA: 4.4% of pioglitazone vs 5.7% of control ($P = 0.005$)
- More CHF in pioglitazone (2.3%) vs control (1.8%) ($P = .002$), no effect on mortality

### Pentoxifylline (PTX) vs Placebo RCTs With Paired Biopsies

<table>
<thead>
<tr>
<th>Primary Outcome and Other Changes from Baseline in Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Total NAS (mean change)</td>
</tr>
<tr>
<td>Steatosis</td>
</tr>
<tr>
<td>Lobular Inflammation</td>
</tr>
<tr>
<td>Hepatocyte ballooning</td>
</tr>
<tr>
<td>Fibrosis stage (0-4)</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; CHF, congestive heart failure; CVA, cerebrovascular accident; MI, myocardial infarction; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

Abbreviations: NAS, nonalcoholic fatty liver disease activity score; RCT, randomized controlled trial.
Drugs for NASH—Who Should Get Which One?

- **Vitamin E**
  - NASH without diabetes
  - Insufficient evidence to treat cirrhotics
  - ? Efficacy in diabetics

- **Pioglitazone**
  - NASH with or without diabetes
  - Limited data in cirrhotics

- **Pentoxifylline**
  - NASH, needs further study to determine efficacy and ideal subpopulation

- **Limitations of available drugs**
  - Effect size in all of these trials is small
  - High placebo response rate

Abbreviation: NASH, nonalcoholic steatohepatitis.

Emerging therapy for NASH

2013

November 2015

8 active clinical trials

265 active clinical trials

Clinicaltrials.gov
### Drugs in Phase II Clinical Trials for NASH

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Preliminary Findings (Positive Pilot Data in NASH)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALT</strong></td>
<td><strong>IR</strong></td>
</tr>
<tr>
<td>Bile acid modifier</td>
<td></td>
</tr>
<tr>
<td>Obeticholic acid **</td>
<td>✓</td>
</tr>
<tr>
<td>TGR-5 agonist INT-777</td>
<td></td>
</tr>
<tr>
<td>FGF 19 agonist NGM 282</td>
<td></td>
</tr>
<tr>
<td>Fatty acid/bile acid modifier</td>
<td></td>
</tr>
<tr>
<td>Aramchol</td>
<td>✓?</td>
</tr>
<tr>
<td>Antioxidant</td>
<td></td>
</tr>
<tr>
<td>SAMe</td>
<td></td>
</tr>
<tr>
<td>PPAR-α/δ agonist</td>
<td></td>
</tr>
<tr>
<td>GFT505</td>
<td>✓</td>
</tr>
<tr>
<td>PDE inhibition/secretion modulation</td>
<td></td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>✓</td>
</tr>
<tr>
<td>Incretin mimetic/GLP-1 agonist</td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>✓</td>
</tr>
<tr>
<td>Liraglutide *</td>
<td>✓</td>
</tr>
<tr>
<td>Lipid modulating</td>
<td>Ezetimibe</td>
</tr>
<tr>
<td>Leptin therapy</td>
<td>Metreleptin</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Bovine hyperimmune globulin</td>
</tr>
<tr>
<td>Pan-caspase inhibition</td>
<td>Emricasan/IDN-6556</td>
</tr>
<tr>
<td>Antifibrotics</td>
<td>Simtuzumab (LOXL2)</td>
</tr>
<tr>
<td></td>
<td>GR-MD-02 (binds galectin)</td>
</tr>
<tr>
<td></td>
<td>CCR2/5 inhibition (Cenicriviroc)</td>
</tr>
</tbody>
</table>

✓ = preliminary study(ies) showing benefit.
Potential effects of FXR agonists in NASH


The FXR Ligand OCA in NASH Treatment (FLINT) Trial

**Design**
- Phase IIb, randomized, double-blind, placebo-controlled study to assess efficacy and safety of OCA 25 mg/d vs placebo in patients with NASH

**Duration**
- 72 weeks OCA 25 mg/d vs placebo

**Patients**
- 283 patients ≥18 years of age
  - Entry criteria
    - Histologic evidence of NASH based on a liver biopsy obtained ≤90 days prior to randomization
    - NAFLD Activity Score (NAS) ≥4

**Endpoints**
- **Primary**
  - Histologic improvement in NAS from baseline to Week 72
  - No worsening in fibrosis; and
  - Decrease in NAS of ≥2 points
- **Secondary**
  - Changes in fibrosis score, hepatocellular ballooning score, liver enzymes, hepatic fat fraction, insulin resistance/sensitivity, bile acid levels

Abbreviations: FXR, farnesoid X receptor; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid.

Neuschwander-Tetri et al. Lancet 2014
FLINT: Effects of OCA on Histology

Primary endpoint: Improved histology
- NAS decrease of ≥2
- No increase in fibrosis

<table>
<thead>
<tr>
<th></th>
<th>OCA 25 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients meeting primary endpoint (%)</td>
<td>46%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Abbreviations: NAS, nonalcoholic fatty liver disease activity score; OCA, obeticholic acid.
Neuschwander-Tetri et al. Lancet 2014

FLINT (N=219)
Secondary Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>OCA 25 mg</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis Improvement (%)</td>
<td>35%</td>
<td>19%</td>
<td>0.01</td>
</tr>
<tr>
<td>Hepatocellular Ballooning (%)</td>
<td>46%</td>
<td>31%</td>
<td>0.03</td>
</tr>
<tr>
<td>Steatosis (%)</td>
<td>61%</td>
<td>38%</td>
<td>0.001</td>
</tr>
<tr>
<td>Lobular Inflammation (%)</td>
<td>53%</td>
<td>35%</td>
<td>0.007</td>
</tr>
<tr>
<td>NASH Resolution (%)</td>
<td>22%</td>
<td>13%</td>
<td>0.09</td>
</tr>
</tbody>
</table>

- For OCA group: all components of NAS improved vs placebo (p-value range: 0.03-<0.001)

Abbreviations: NAS, nonalcoholic fatty liver disease activity score; OCA, obeticholic acid.
Neuschwander-Tetri et al. Lancet 2014
Lipid Concentrations

1: Data from Neuschwander-Tetri et al. *The Lancet* and Supplementary Appendix. Published online November 7, 2014. 2: All p-values compared to placebo. *p<0.05  3: Converted mean values using factor of 38.6 for cholesterol and 88.5 for triglycerides.

Potential issues with OCA: Safety and Tolerability

- **Pruritus:**
  - OCA group (23%) vs placebo (6%)
  - Higher grade (predominantly moderate pruritus)
  - 1 discontinuation of OCA due to pruritus
- ? Cardiovascular impact of lipid changes

### PPARs as Targets for NASH

<table>
<thead>
<tr>
<th>PPAR-α</th>
<th>PPAR-γ</th>
<th>PPAR-α/δ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-oxidation:</strong></td>
<td><strong>Steatosis</strong></td>
<td><strong>β-oxidation</strong></td>
</tr>
<tr>
<td><strong>↓</strong></td>
<td><strong>↓</strong></td>
<td><strong>↓</strong></td>
</tr>
<tr>
<td><strong>Less Effective in Humans</strong></td>
<td><strong>Insulin Sensitivity</strong></td>
<td><strong>Hepatic Steatosis</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Inflammation</strong></td>
<td><strong>Insulin Sensitivity</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Fibrosis</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Dyslipidemia</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Clinical Data in MetS</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Preclinical Data in NASH</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Safety Concerns</th>
</tr>
</thead>
</table>

Abbreviations: MetS, metabolic syndrome; NASH, nonalcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor.


### Background

**Elafibranor is a dual PPARα/δ agonist with no PPARγ activity**

<table>
<thead>
<tr>
<th>Phase 2a trials</th>
<th>Phase 2a trials</th>
<th>Disease models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement of glucose homeostasis and insulin sensitivity</td>
<td>Improvement of liver dysfunction markers</td>
<td><strong>Efficacy in NASH acting on:</strong></td>
</tr>
<tr>
<td>Favorable effects on lipids:</td>
<td></td>
<td>- Steatosis</td>
</tr>
<tr>
<td>- Decreases TG</td>
<td></td>
<td>- Inflammation</td>
</tr>
<tr>
<td>- Increases HDL-C</td>
<td></td>
<td>- Hepatocyte injury</td>
</tr>
<tr>
<td>- Increases LDL-C</td>
<td></td>
<td>- Fibrosis</td>
</tr>
</tbody>
</table>

**GOLDEN 505 IN NASH**

<table>
<thead>
<tr>
<th>Phase 2a trials</th>
<th>Phase 2a trials</th>
<th>Phase 2a trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of safety concern</td>
<td>Anti-inflammatory properties</td>
<td></td>
</tr>
</tbody>
</table>


Courtesy of V Ratziu
**GOLDEN 505 trial (Elafibranor)**

International trial in NASH: 56 sites (US + 8 European countries) Total ITT population: N=274

**Inclusion**
- Liver Biopsy
- End-of-treatment
- Liver Biopsy

**Main Inclusion criteria**
- Non-cirrhotic NASH : NAS≥3 with at least 1 in steatosis, ballooning and inflammation, T2DM stratified

**Primary outcomes**
- Resolution of NASH without worsening of fibrosis (% in Elafibranor treated groups vs % in placebo)


![Diagram](https://via.placeholder.com/150)

**Resolution of NASH + no worsening of fibrosis, ITT (N=274)**

<table>
<thead>
<tr>
<th>Protocol Defined Primary Endpoint (% responders)</th>
<th>Placebo (N92)</th>
<th>Elafibranor 80 mg (N93)</th>
<th>Elafibranor 120 mg (N89)</th>
<th>OR*</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>17%</td>
<td>23%</td>
<td>21%</td>
<td></td>
<td>1.53</td>
<td>(0.70-2.34)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

**Updated Definition, (% responders)**

<table>
<thead>
<tr>
<th>Placebo (N92)</th>
<th>Elafibranor 80 mg (N93)</th>
<th>Elafibranor 120 mg (N89)</th>
<th>OR*</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>12%</td>
<td>13%</td>
<td>19%</td>
<td></td>
<td>2.31</td>
<td>(1.02-5.24)</td>
</tr>
</tbody>
</table>

* 120 mg vs. placebo

Courtesy of V Ratziu
### Histological secondary end-points, ITT (N=274)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline severity, bNAS (%)</th>
<th>Placebo 120mg, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NAS 2 point reduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (6-8), N=90</td>
<td>23</td>
<td>40</td>
</tr>
<tr>
<td>Moderate (4-5), N=144</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>Mild (3), N=40</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td><strong>Steatosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (6-8), N=90</td>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td>Moderate (4-5), N=144</td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>Mild (3), N=40</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td><strong>Hepatocyte ballooning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (6-8), N=90</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>Moderate (4-5), N=144</td>
<td>29</td>
<td>33</td>
</tr>
<tr>
<td>Mild (3), N=40</td>
<td>38</td>
<td>21</td>
</tr>
<tr>
<td><strong>Lobular inflammation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (6-8), N=90</td>
<td>39</td>
<td>53</td>
</tr>
<tr>
<td>Moderate (4-5), N=144</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>Mild (3), N=40</td>
<td>44</td>
<td>14</td>
</tr>
</tbody>
</table>


---

### Resolution of NASH is associated with Fibrosis reduction

Responders vs Non-Responders for the primary endpoint in completers on 120 mg (N=78)

![Graph showing resolution of NASH components](image)


Courtesy of V Ratziu
**Changes in HgbA1c and glucose homeostasis in T2D**

Elafibranor 120 mg (N=35); Placebo group (N=28)

Significant decrease in HbA1C and overall improvement of glucose homeostasis and insulin sensitivity obtained on top of concomitant anti-diabetic treatments.


**Changes in plasma lipids relative to baseline**

Elafibranor 120 mg vs placebo

The effect size vs placebo was calculated and expressed as LSMean±Standard Error. *p<0.05, **p<0.01, ***p<0.001 vs placebo.

Highly significant improvement of all components of plasma lipid profile

Courtesy of S Harrison
Effects of Elafibranor on NASH: Summary

- Elafibranor (dual PPAR α/δ agonist) demonstrated histologic efficacy in patients with NASH
- Resolution of NASH (without worsening of fibrosis) was achieved by the 120 mg dose in the population of patients with moderate/severe NASH activity (baseline NAS ≥4)
- Resolution of NASH was associated with improvement in fibrosis
- 120 mg was well tolerated
- Favorable cardiometabolic effects
- Phase 3 trial is planned for 2016


Evolving treatment for advanced disease

- HCC risk
- CVD risk
- Hepatic decompensation
- Reduction in PHTN
- Reduction in fibrosis
- Decreased decompensation
- Improved survival
Reversibility of Fibrosis

![Diagram of liver fibrosis with text on injury and inflammation, removal of pre-fibrotic stimulus, antifibrotic therapy, and MMP activation]


HVPG and MELD > 10 predict decompensation

![Graphs showing cumulative probability of clinical decompensation for HVPG and MELD]

Ripoll et al. Gastroenterology 2007
Antifibrotics in Clinical Trials

- **LOXL2 inhibition**\(^1,2\)
  - Inhibits cross-linking of collagen in pathologic stroma
  - Levels may correlate with extent of fibrosis and clinically relevant endpoints (IPF)
  - Very limited preliminary data
- **Cenicriviroc (CCR2/5 inhibitor)**
  - Phase 2 completed for NASH
- **Galectin inhibition**\(^3\)
  - Animal data in NASH models

Abbreviations: IPF, idiopathic pulmonary fibrosis; LOXL2, lysyl oxidase-like 2; NASH, nonalcoholic steatohepatitis.


---

**Lysyl Oxidase-Like 2 (LOXL2) Fibrosis Pathway**

- Catalyze the first step in the cross linking of collagen
- LOXL2 is involved in extra cellular matrix modeling and fibrosis

[Diagram showing the LOXL2 fibrosis pathway with reactions and molecules involved in collagen and elastin cross-linking.]

**Efficacy of Anti-LOXL2 in CCl4-Induced Fibrosis**


**Simtuzumab: Ongoing RCTs for NASH with advanced fibrosis**

- **Primary endpoint**: Histology (Δ % collagen area on liver biopsy)
- **Secondary endpoints**: noninvasive assessments, exploratory biomarkers
- **Prevention of progression to cirrhosis**

- **Primary endpoint**: HVPG
- **Secondary endpoints**: Histology (Δ % collagen), noninvasive assessments, exploratory biomarkers
- **Demonstrate clinical benefit** (death, transplant, decompensation) at year 5
Thank you
Question 1:

Which of the following patients would be appropriate for liver biopsy to exclude NASH in the setting of suspected NAFLD?

A. 65 y/o obese female with diabetes, HTN, dyslipidemia and normal liver enzymes
B. 65 y/o obese female with diabetes, HTN, dyslipidemia and elevated liver enzymes
C. 25 y/o woman with PCOS and persistently elevated liver enzymes
D. 25 y/o woman with PCOS, normal liver enzymes
E. All of the above
F. B and D
G. A-C

Answer: G

Age, diabetes and hypertension are the strongest predictors of advanced disease in patients with NAFLD, irrespective of liver enzyme elevation. PCOS is characterized by insulin resistance and associated with NAFLD and increased risk for NASH. Beyond its association with NAFLD and NASH biopsy is indicated in any patient with persistently elevated unexplained elevation in liver chemistry tests.(Ref Ratziu 2005, Angulo and AASLD practice guidelines 2012)

Question 2:

NASH is associated with increased mortality compared to general population. What is the most common cause of death?

A. Liver disease
B. Cardiovascular disease
C. Hepatocellular carcinoma
D. Death from cardiovascular disease, malignancy, and liver disease are equivalent

Answer: B

Based on population based studies, cardiovascular disease is the most common cause of death in patients with NAFLD. Next is malignancy (not limited to Hepatocellular cancer) with liver related death coming in third as cause of death in patients with NAFLD. Refs: Rafiq et al. Clin Gastro Hep 2009; Ekstedt et al 2014; Dam-Larsen et al., Scand J of Gastroenterol 2009)
Question 3:

Which of the following methods can provide an accurate diagnosis of NASH in a patient with NAFLD?

A. MRI Elastography  
B. CK-18 levels  
C. Ultrasound  
D. Liver biopsy  
E. B and D

Answer: D
At this point only liver biopsy can make a diagnosis of NASH. While CK-18 has modest accuracy in correlating with NASH on biopsy, studies have used different cut-off points to make this determination. MRE assesses hepatic stiffness and is useful to diagnose advanced fibrosis.

Question 4:

Making the diagnosis of cirrhosis in a patient with NAFLD changes clinical practice in which of the following ways?

A. Triggers bi-annual screening for hepatocellular carcinoma  
B. Changes frequency of colorectal cancer screening to every 5 years  
C. Initiates variceal screening with upper endoscopy  
D. All of the above  
E. A and C

Answer: E
When the diagnosis of cirrhosis is made all patients need to be screened for liver cancer and esophageal varices. While overall malignancy is higher in patients with NAFLD, screening for colon cancer does not change unless dictated by the presence of another risk factor i.e. Primary Sclerosing Cholangitis.
Question 5:

Which of the following modalities is well studied in patients with NAFLD and can be reliable for the diagnosis of cirrhosis?

A. MRI elastography  
B. Ultrasound  
C. Fibroscan  
D. None of the above

Answer: A  
Only MRE is well studied in NAFLD and in the absence of known confounders effecting liver stiffness i.e. right heart failure, it is sufficiently accurate to make the diagnosis of cirrhosis. Fibroscan is well studied in HCV but much less so in NAFLD and its accuracy may be effected by hepatic fat content. Standard ultrasound cannot quantify liver stiffness.

Question 6:

Which of the following treatments – established and in phase 2 trials has demonstrated an improvement in fibrosis in patients with NASH?

A. Weight loss  
B. Vitamin E  
C. Obeticholic acid (OCA)  
D. Pioglitazone  
E. All of the of the above  
F. A and C  
G. A-C

Answer: F  
Only weight loss (both in dietary and bariatric surgery induced) and OCA have demonstrated anti-fibrotic efficacy in phase 2 trials. Neither B=Vitamin E or pioglitazone resulted in improved fibrosis (PIVENS trial), though meta-analysis did suggest improvement.)