HEPATOLOGY UPDATE
NEW DEVELOPMENTS IN PBC, NAFLD & NASH

TUESDAY, OCTOBER 27, 2015
FIRA DE BARCELONA

Supported by an educational grant from Intercept Pharmaceuticals, Inc.
Jointly provided by the Annenberg Center for Health Sciences at Eisenhower and the Chronic Liver Disease Foundation.
This symposium is not affiliated with UEG.
7:00 AM  WELCOME & OPENING REMARKS
Michael Trauner, MD

7:05 AM  PBC: CLINICAL UPDATE & CASE DISCUSSION
David E. J. Jones, MD, PhD

7:30 AM  NAFLD & NASH: CLINICAL UPDATE & CASE DISCUSSION
Zobair M. Younossi, MD, MPH

7:55 AM  CLOSING REMARKS
Michael Trauner, MD
Educational Objectives

Upon completion of this educational activity, participants should be able to:

- Develop an evidence-based treatment regimen using the latest clinical evidence
- Explain the current and emerging treatment options for patients with NAFLD/NASH and PBC
- Recognize and communicate the risks and benefits of current and emerging treatment options
- Identify barriers to the optimal management of patients with NAFLD/NASH and PBC
The Chronic Liver Disease Foundation would like to thank **Intercept Pharmaceuticals, Inc.** for providing an educational grant to support this educational program.
Hepatology Update: New Developments in PBC and NASH

Michael Trauner, MD
Professor of Medicine
Chair, Division of Gastroenterology and Hepatology
Medical University of Vienna
Vienna, Austria
Impact of Liver Disease on Society

- Liver disease is a major cause of morbidity and mortality in EU
  - Affects 6% of EU population\(^1\)
  - Eventually leads to cirrhosis, HCC, and liver transplantation (NASH 2\(^{nd}\) leading indication)
  - >5,500 liver transplantations in EU per year\(^2\)
  - Liver cancer causes \(\sim47,000\) deaths in EU per year\(^2\) (2\(^{nd}\) leading cause of cancer mortality)
  - Liver disease is 5\(^{th}\) most common cause of death in EU (1 in 6)\(^1\)

- NASH is emerging as major cause of advanced liver disease (including HCC) in general population
  - Prevalence of NAFLD is up to 44% in EU\(^2\)

- Incidence of PBC in EU is growing\(^2,3\)
  - More than doubled over past 10 years

Abbreviations: EU, European Union; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis.
Rationale for Focus on PBC and NASH

- PBC and NASH are important from a public health standpoint and their impact on individual patients
  - Divergent burden of disease between PBC and NASH
- Major recent advances in these two liver diseases
  - Understanding the role of bile acids in the pathobiology has helped to identify novel therapeutic targets
- Evolution in the ways we assess these patients
  - Disease heterogeneity → individual course may vary
  - Urgent need for non-invasive biomarkers
  - Currently no reliable biomarkers to assist in stratification and prognosis
- Gaps in early diagnosis and treatment of PBC & NASH

Abbreviation: NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis.
PBC Focus

- Understanding of PBC pathophysiology and its therapeutic options have evolved
- Substantial proportion of patients are refractory to available treatment, indicating need for new therapies
  - New therapies (beyond UDCA) are under investigation
  - Response-guided therapy
- Identification and utilization of appropriate endpoints is critical
  - Clinical, surrogate, and patient-reported outcomes, such as fatigue and quality of life
- Clinician awareness is needed for effective PBC therapy

Abbreviation: PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.
Increasing prevalence demands effective new therapies
  – Clinical, economic & quality of life burden to patients & society

New therapeutic options are based on better understanding of targets related to NASH pathophysiology
  – Multiple factors may have a role in NASH
    – Insulin resistance, lipotoxicity, oxidative stress & dysbiosis

Treatment must be individualized and based on liver disease stage (fibrosis) and metabolic comorbidities

Noninvasive methods to track disease progression and measure treatment response are urgently needed

Closing gap between knowledge and treatment implementation is essential

Abbreviation: NASH, nonalcoholic steatohepatitis.
Clinical Update in PBC

The Dawn of Stratified Therapy

David E. J. Jones, MD, PhD
Newcastle University
PI UK-PBC Research Consortium
Newcastle upon Tyne, United Kingdom
Case 1

- 65 year old woman
- Minimally abnormal LFTs at “well-woman” clinic, mild fatigue, mild itch
- AMA +ve at 1:640, liver biopsy showed stage I PBC
- Started UDCA
- 12 months later LFTs normal and itch resolved
Case 2

- 37 year old woman
- Profound fatigue, Alk Phos 630, ALT 122
- AMA +ve at 1:320, ANA 1:80, liver biopsy showed stage 2 PBC with marked interface hepatitis
- Started UDCA
- 12 months later Alk Phos 488, ALT 98, bilirubin 19, fatigued
- Very worried about the future, being considered for OCA trial
Case 1

The “traditional” view of PBC

• Mild disease in an elderly woman
• Mild itch as the symptom
• Responds well to UDCA
• Risk very low and unlikely to die of liver disease or need transplant
PBC as seen in our clinic in 2015

- Aggressive disease in a young woman or man
- Fatigue as a prominent or even life altering feature
- Minimal response to UDCA (and no symptom improvement)
- Sp100/Gp210 ANA and interface hepatitis
- High risk of need for transplant
- Needs second line therapy
Stratified Medicine in PBC
The UK-PBC Research Consortium

• 6700 PBC patients across all trusts in the UK

• Detailed genotyping and phenotyping
  – Response/Non-response to therapy
  – Transplant need
  – Symptoms

• Extended tissue phenotyping of “high risk patients”
  – Proven UDCA non-responders
  – New presenters at high risk of non-response (<50)

• Unique clinical trials platform
Survival is Still Significantly Impaired in PBC in the UDCA Era

Transplant-free survival of all NE1-25 cohort PBC patients vs case controls

Abbreviations: PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.

Suboptimal Therapy in PBC—What Are the Potential Causes?

- Drugs are not as effective as we think they are and/or our biomarkers of response don’t accurately predict real response
- Effectiveness may not be as universal as we think it is
- Drugs are effective but we aren’t using them optimally
- Drugs are effective but aren’t actually getting to people
- Some combination of the above
Suboptimal Therapy in PBC - The Simple Causes

- In UK-PBC national cohort, 20% of PBC patients are not treated with urso-deoxycholic acid (UDCA)
- Significant percentage of patients are treated with doses in 10- to 12-mg/kg range
- Some issues with adherence (weight gain, nausea, hair loss?)
- Simple and consistent message is needed about UDCA
## Criteria for “Response” to UDCA in PBC

<table>
<thead>
<tr>
<th>Paris Criteria</th>
<th>Barcelona Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bilirubin ≤1 mg/dL + AST ≤2 x ULN + ALP ≤3 x ULN after 12/12 UDCA at 13-15 mg/kg</td>
<td>• ALP decrease by 40% or normalized After 12/12 UDCA at 13-15 mg/kg</td>
</tr>
<tr>
<td>• <strong>Responder</strong>: 96% survival vs 99% control population at 5 years</td>
<td></td>
</tr>
<tr>
<td>• <strong>Nonresponder</strong>: 69% survival vs 68% Mayo Predicted Survival</td>
<td></td>
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</tbody>
</table>

### Issues

- Reciprocity
- “Virtual” controls (the 65-year-old woman paradox)
- Generalizability
- Dichotomizes a continuous variable

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

UDCA-Response Criteria in the UK-PBC Patient Cohort—Independent Validation

RESULTS: Log-rank test for time free from LT for PBC, PBC-related death or Bilirubin ≥100µmol/L

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Chi-square statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barcelona</td>
<td>7.3</td>
<td>6.73E-03</td>
</tr>
<tr>
<td>Paris I</td>
<td>106</td>
<td>&lt;1E-16</td>
</tr>
<tr>
<td>Toronto</td>
<td>24.2</td>
<td>8.78E-07</td>
</tr>
<tr>
<td>Paris II</td>
<td>45.7</td>
<td>1.40E-11</td>
</tr>
</tbody>
</table>

Abbreviations: LT, liver transplant; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.
### Multivariate time-to-event analysis (baseline variables only)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>SE</th>
<th>HR</th>
<th>L95</th>
<th>U95</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>-0.086</td>
<td>0.035</td>
<td>0.918</td>
<td>0.857</td>
<td>0.983</td>
<td>0.014</td>
</tr>
<tr>
<td>Creatinine</td>
<td>-0.0158</td>
<td>0.005</td>
<td>0.984</td>
<td>0.975</td>
<td>0.994</td>
<td>0.001</td>
</tr>
<tr>
<td>LN Bilirubin</td>
<td>1.407</td>
<td>0.15</td>
<td>4.085</td>
<td>3.046</td>
<td>5.477</td>
<td>&lt;2e-16</td>
</tr>
<tr>
<td>LN (AST or ALT ratio)</td>
<td>-0.53</td>
<td>0.164</td>
<td>0.588</td>
<td>0.427</td>
<td>0.811</td>
<td>0.001</td>
</tr>
<tr>
<td>LN ALP</td>
<td>0.477</td>
<td>0.152</td>
<td>1.611</td>
<td>1.195</td>
<td>2.172</td>
<td>0.002</td>
</tr>
<tr>
<td>Platelets</td>
<td>-0.004</td>
<td>0.002</td>
<td>0.996</td>
<td>0.993</td>
<td>0.999</td>
<td>0.006</td>
</tr>
</tbody>
</table>

### Multivariate time-to-event analysis (including "Paris I response" at 12 months)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>SE</th>
<th>HR</th>
<th>L95</th>
<th>U95</th>
<th>P</th>
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<td>Baseline</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>-0.076</td>
<td>0.031</td>
<td>0.927</td>
<td>0.871</td>
<td>0.986</td>
<td>0.016</td>
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<tr>
<td>LN Bilirubin</td>
<td>1.157</td>
<td>0.139</td>
<td>3.181</td>
<td>2.423</td>
<td>4.177</td>
<td>&lt;2e-16</td>
</tr>
<tr>
<td>LN (AST or ALT ratio)</td>
<td>-0.455</td>
<td>0.165</td>
<td>0.634</td>
<td>0.459</td>
<td>0.877</td>
<td>0.006</td>
</tr>
<tr>
<td>Platelets</td>
<td>-0.003</td>
<td>0.001</td>
<td>0.997</td>
<td>0.994</td>
<td>0.999</td>
<td>0.020</td>
</tr>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment failure</td>
<td>2.124</td>
<td>0.308</td>
<td>8.361</td>
<td>4.574</td>
<td>15.278</td>
<td>5.10E-12</td>
</tr>
</tbody>
</table>

The UK-PBC Continuous Risk Model

**Alkaline Phosphatase**

**Alanine Transaminase**

**Bilirubin**

**Albumin**

**Platelet Count**
The UK-PBC Continuous Risk Model

A= <25th Centile
B=25th-50th Centile
C=50th-75th Centile
D=75th-90th Centile
E=>90th Centile

UDCA has a beneficial effect in 166/1000 patients with PBC in the UK-PBC cohort. For every 100 genuine responders, there are 96 genuine nonresponders.
>50% of patients in the UK-PBC patient cohort who presented before the age of 50 have failed primary therapy (in a state of UDCA nonresponse or already transplanted) by the time of study.

Potential Mechanisms for UDCA Non-response in PBC and Possible Options for Therapeutic Advance

- Different severity or nature of immune response
  - Targeted immunosuppression (biologics)
- Different bile pool/microbiota
  - “Second-line” bile acid therapies
- Different biliary epithelial response
  - Biliary epithelial protectant agents
- Pre-existing fibrosis/cirrhosis
  - Earlier diagnosis allowing treatment window for UDCA!
  - Antifibrotics

Abbreviations: PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.
Challenges for Trial Design for Second-Line Therapy in PBC

- Definition of the “at-risk” population requiring second-line therapy
- Outcome measures (do UDCA response criteria apply to other therapies?)
- Lack of relevant biomarkers
- Impossibility of carrying out a hard endpoints trial due to prolonged disease
- Difficulty in performing a histology-based trial (acceptability and lack of scoring systems)
- “Phasing” of therapy use
Drugs Under Evaluation for Second-Line Therapy in PBC

- Rituximab (B-cell depletion)
- Fibrates (PPAR-α agonists)
- Obeticholic acid (6-ethyl chenodeoxycholic acid, FXR agonist)
- Nor-ursodeoxycholic acid (bicarbonate “umbrella,” anti-inflammatory, anti-fibrotic)
Fenofibrate Improves Liver Biochemistry Values in PBC Patients

- Peroxisome proliferator-activated receptor (PPAR)-α agonist, fibric acid derivative
- PPAR-α activity
  - Regulation of bile acid synthesis and detoxification
  - Modulates phospholipid secretion, which helps protect bile duct epithelium by formation of micelles
- Open-label study to evaluate 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 hepatic or severe renal dysfunction, including PBC
PPAR-α Agonism as a Therapeutic Option in PBC-Bezafibrate

PPAR-α Agonism as a Therapeutic Option in PBC-Bezafibrate

- 27 patients enrolled refractory to UDCA and with dyslipidaemia
- UDCA versus UDCA + BF
- FU 017 & 110 months
- Significant improvement in AP
- Significant deterioration in creatinine
- No difference in outcome
FXR-Agonism as a Therapeutic Option in PBC-Properties of Obeticholic Acid

- Shared properties with ursodeoxycholic acid (UDCA)
  - Choleresis
  - Antiapoptosis
  - Antioxidant

- Additional direct properties
  - Induced bile acid detoxification
  - Induced bile acid conjugation
  - Suppressed bile acid synthesis
  - Modified bile acid transport

- Additional indirect properties (via GI release of FGF-19)
  - Suppressed bile acid synthesis

*Could “UDCA nonresponse” addressed by OCA be a manifestation of indirect actions?*
Primary efficacy endpoint was percent change in plasma ALP from pretreatment values; patients with a placebo-subtracted ALP reduction of ≥10% were defined as responders.

Abbreviations: ET, end of treatment; FXR, farnesoid X receptor; OCA, obeticholic acid; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.

Abbreviations: ET, end of treatment; FXR, farnesoid X receptor; OCA, obeticholic acid; PBC, primary biliary cirrhosis.
Hirschfield G et al., Gastroenterology, 2015, 148: 751-761.
FXR-Agonism as a Therapeutic Option in PBC—Obeticholic Acid (INT-747)

*Phase III (POISE)*

**N=216**

- **Continue pre-study UDCA**
- **Placebo**
  - **OCA 10 mg**
  - **OCA 5 mg**

**All Patients (N=180) Long-term Safety Extension**
- 5 years OCA Rx

**Entry**
- ALP $\geq 1.67 \times$ ULN and/or bilirubin > ULN but <2 x ULN

**Positive Response**
- ALP <1.67 x ULN and bilirubin WNL, and $\geq$15% ALP reduction

**Screening**
- 0  W2  M3  M6  M9  M12

1 to 8 weeks

$\uparrow$  $\uparrow$  $\uparrow$  $\uparrow$  $\uparrow$  $\uparrow$

& LTSE Visit 1

**Abbreviations:** ALP, alkaline phosphatase; FXR, farnesoid X receptor; LTSE, long-term safety extension; OCA, obeticholic acid; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; WNL, within normal limits.

**FXR-Agonism as a Therapeutic Option in PBC—Obeticholic Acid (INT-747) Phase III Data (POISE)**

### Primary Endpoint:
Proportion of subjects achieving ALP $<1.67 \times$ ULN with bilirubin $\leq$ULN and $\geq15\%$ reduction in ALP

*P*<.0001 vs placebo; *P*-values obtained using Cochran-Mantel-Haenszel stratified by randomization strata factor.

Abbreviations: ALP, alkaline phosphatase; FXR, farnesoid X receptor; OCA, obeticholic acid; PBC, primary biliary cirrhosis; ULN, upper limit of normal.

FXR-Agonism as a Therapeutic Option in PBC—Obeticholic Acid (INT-747)

Phase III Data (POISE)

$P<.0001$ vs placebo for all post baseline values of titrated OCA and 10 mg OCA groups.

Abbreviations: ALP, alkaline phosphatase; FXR, farnesoid X receptor; LS, least squares; OCA, obeticholic acid; PBC, primary biliary cirrhosis; SE, standard error.

FXR-Agonism as a Therapeutic Option in PBC—Obeticholic Acid (INT-747)

Phase III Data (POISE)

\[ \text{LS Mean (SE) in ALT (U/L) from baseline} \]

- Placebo (n=73)
- Titrated OCA (n=70)
- 10 mg OCA (n=73)

\( P < 0.0001 \) vs placebo for all post baseline values of titrated OCA and 10 mg OCA groups.

Abbreviations: ALT, alanine aminotransferase; FXR, farnesoid X receptor; LS, least squares; OCA, obeticholic acid; PBC, primary biliary cirrhosis; SE, standard error.

FXR-Agonism as a Therapeutic Option in PBC—Obeticholic Acid (INT-747)

Phase III Data (POISE)

Abbreviations: FXR, farnesoid X receptor; LS, least squares; OCA, obeticholic acid; PBC, primary biliary cirrhosis; SE, standard error.

FXR-Agonism as a Therapeutic Option in PBC—Obeticholic Acid (INT-747)  
*Phase III Data (POISE)*

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=73)</th>
<th>Titrated OCA (n=70)</th>
<th>10 mg OCA (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D/C due to pruritus, n (%)</td>
<td>0</td>
<td>1 (1%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>TEAEs without pruritus, n (%)</td>
<td>66 (90%)</td>
<td>62 (89%)</td>
<td>63 (86%)</td>
</tr>
<tr>
<td>TEAE pruritus, n (%)</td>
<td>28 (38%)</td>
<td>39 (56%)</td>
<td>50 (68%)</td>
</tr>
<tr>
<td>SAEs, n (%)</td>
<td>3 (4%)</td>
<td>11 (16%)</td>
<td>8 (11%)</td>
</tr>
</tbody>
</table>

Abbreviations: D/C, discontinuation; FXR, farnesoid X receptor; OCA, obeticholic acid; PBC, primary biliary cirrhosis; SAE, serious adverse event; TEAE, treatment-emergent adverse effect.

Clinician Awareness is a Challenge for Effective Therapy in PBC

<table>
<thead>
<tr>
<th></th>
<th>Responders (%)</th>
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</thead>
<tbody>
<tr>
<td>Hephs</td>
<td>80</td>
</tr>
<tr>
<td>Gastroenterologists</td>
<td>65</td>
</tr>
<tr>
<td>Competence:</td>
<td></td>
</tr>
<tr>
<td>&quot;Highly Competent&quot;</td>
<td></td>
</tr>
<tr>
<td>Early Diagnosis</td>
<td>88</td>
</tr>
<tr>
<td>Gastroenterologists</td>
<td>87</td>
</tr>
<tr>
<td>Practice Performance:</td>
<td>&quot;Always/Often&quot;</td>
</tr>
<tr>
<td>Early Diagnosis</td>
<td>76</td>
</tr>
<tr>
<td>Gastroenterologists</td>
<td>65</td>
</tr>
</tbody>
</table>

Abbreviations: gastro, gastroenterologist; hep, hepatologist; PBC, primary biliary cirrhosis
Clinician Competence in and Use of Response Criteria for Assessing Treatment Response in PBC

Competence: “Highly Competent”

Responders (%)

<table>
<thead>
<tr>
<th></th>
<th>Heps</th>
<th>Gastro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepes</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Gastros</td>
<td>30</td>
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Practice Performance: “Always/Often”

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<tr>
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<th>Heps</th>
<th>Gastro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepes</td>
<td>76</td>
<td></td>
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<tr>
<td>Gastros</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: gastro, gastroenterologist; hep, hepatologist; PBC, primary biliary cirrhosis
Slide courtesy of David E. J. Jones, MD, PhD.
Overall Health and Quality of Life
UK-PBC Cohort Data (n=2300)

Individual Symptom Domain Impacts UK-PBC Cohort Data (n=2300)

Reaching the Goal—What We Need to Do to Improve PBC Care

- Improve community, patient, and first responder awareness of the disease and its presentations
- Improve physician awareness of the need for therapy with UDCA and assessment of response
- Systematic approach to management with triage built in for high-risk/nonresponding patients
- Systematic approach to the evaluation of second-line therapy and implementation into stratified management pathways
- Improved awareness of, assessment of, and treatment of symptoms in PBC using systematic approaches
All patients with suspected PBC should have an abdominal ultrasound as part of their baseline assessment (standard 90%).

UDCA at 13-15mg/kg/day is recommended for first-line use in all patients with PBC (standard 90% of patients receiving therapy at adequate dose or documented to be intolerant).

Individualised risk stratification using biochemical response indices is recommended following one year of UDCA therapy (standard 80% of patients receiving UDCA therapy to have their response status recorded in the notes and the criteria used recorded).

All patients should be evaluated for the presence of symptoms, particularly fatigue and itch (standard 90% of patients have the presence/absence of fatigue and pruritus recorded in the notes in the last year).

All patients with a bilirubin >50 or evidence of decompensated liver disease should be discussed with a hepatologist linked to a transplant programme (standard 90% documentation that discussion has taken place within 3 months of the bilirubin exceeding 50 and the actions taken recorded).

All patients with PBC should have a risk assessment for osteoporosis. Treatment and follow-up should be according to national guidelines (standard 80% assessment within the Last 3 years).

Overlap with autoimmune hepatitis is rare and when suspected, liver biopsy, with expert clinico-pathological assessment, is recommended to make the diagnosis (standard 90% of patients in whom the diagnosis of overlap is made having liver biopsy confirmation and the CPC discussion noted).
PBC

Audience Questions
Mrs. S is a 64 year old female who presents for persistent elevation of aminotransferases. She complains of fatigue and arthritis in her knees. She is often sleepy when she wakes. Allergies: NKDA. Meds: lisinopril, simvastatin, metformin, H2-blockers, multivitamin, Liv52 supplement. Past medical history: Diabetes, hypertension, hypercholesterolemia, GERD, arthritis. Family history: No liver disease, liver cancer or cirrhosis. Mother and sister have diabetes. Mother had a heart attack at age 66. Social history: Nonsmoker. Retired teacher. Has half a glass of wine on special occasions. Does not exercise regularly. Walks with her husband “when it’s nice out.” Physical exam is unremarkable overall, except for obesity and skin findings of acanthosis nigricans. Blood pressure: 139/84. Weight: 91 kg, height: 170 cm, BMI: 31.32 kg/m². Waist circumference: 112 cm.
Case Presentation

- CBC normal except for platelets: 146,000
- Albumin (3.6 - 5.1 g/dL): 4.3, 4.1
- Bilirubin, Total (0.2 - 1.2 mg/dL): 0.6, 0.9
- AST (10 - 40 U/L): 65, 120
- ALT (9 - 46 U/L): 75, 112
- Alkaline Phosph (40 - 115 U/L): 91, 93
- HCV Ab & HBs Ag: Negative
- ASMA, AMA, ANA: Negative
- Iron saturations: 28%
- Ferritin: 446
- Alpha 1 antitrypsin: 249
- Abdominal ultrasound shows increased liver echotexture suggestive of fatty liver
- Fibroscan inconclusive (technically limited due to increased body habitus)

WHAT SHOULD WE DO NEXT?
Case Presentation: Liver Biopsy Results

• Microscopic Description
  – Sections obtained after processing show a 17 mm long liver biopsy containing more than 11 portal tracts. The biopsy shows steatosis with scattered lobular and portal inflammation and prominent hepatocellular ballooning with a number of Mallory bodies, indicating an active steatohepatitis. The trichrome stain shows extensive centrilobular pericellular fibrosis as well as several areas of bridging fibrosis.

• Diagnosis
  – STEATOHEPATITIS, NONALCOHOLIC BY HISTORY, WITH BRIDGING FIBROSIS
What is NAFLD?

Histologically, NAFLD Represents a Spectrum

- Exclusion of liver diseases (HCV & ETOH)
- Requires specific pathologic criteria for NASH
- 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 (N=8,515,431 from 22 countries)
- Global prevalence of NAFLD is 21.48% (18.35-24.99) with highest prevalence in Middle East and South America (30-31%) and lowest in Africa (13.48%)
- The prevalence in North America and Europe is 18.5-20%

Risk Factors

- Metabolic comorbidities associated with NAFLD:
  - Obesity [47.97% (37.20-58.92%)]
  - Type 2 diabetes [20.36% (15.91-25.66%)]
  - Hyperlipidemia [69.16% (49.91-83.46%)]
  - Hypertension [39.14% (33.15-45.48)]
  - Metabolic syndrome [45.05% (34.67-55.88%)]

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

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 & other CLD
- Prevalence of NAFLD in obese and overweight: 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&ALT
- Compared to their own controls, lean NAFLD has more IR and DM

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

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
- Multilevel logistic regression model identified demographic, clinical, comorbidity, and health-care utilization factors associated with recognition and receipt of early NAFLD care


NAFLD Case Definition (n=251)

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistently increased ALT</td>
</tr>
<tr>
<td>No viral hepatitis</td>
</tr>
<tr>
<td>No excessive alcohol (2 yr prior)</td>
</tr>
<tr>
<td>Metabolic syndrome, BMI ≥30</td>
</tr>
</tbody>
</table>

Of patients with NAFLD (N=251)
- 39.4% with recognition of ALT increase
- 21.5% received diagnosis of 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

Only magnitude of ALT elevation (ALT >80 IU/ml vs. <80 IU/ml): AOR=4.4 (2.65–7.30) and proportion of elevation (>50% vs. <50% of ALT values >40 IU/ml): AOR=1.8 (1.03–3.14) were associated with receiving specified NAFLD care.
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>

What Are the Clinical Predictors of Mortality In NAFLD?

- Histologic NAFLD (N=289)
- Clinico-demographic data from the time of biopsy
  - NASH patients were predominantly female, had higher AST, ALT and higher fasting serum glucose
- Mortality: During median follow-up of 150 months
  - NASH patients had higher risk of liver-related mortality than non-NASH NAFLD (p-value = 0.0026)

<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>Type II diabetes</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>

Progression is Based on Histology

NASH is the Subtype of NAFLD that Primarily Progresses

NAFL

NAFLD

NASH

Stable

Liver Failure

Cirrhosis

HCC

(Annual incidence 2%)

Death

80-90%

10-20%

10-15%

65-75%

20-30%

40-60%

Estimate for Disease and Mortality Burden

NAFL
- 51-57 million

NAFLD
- 63 million

NASH
- 6.3-12.6 million

Stable

Liver Failure
- 500,000-700,000

HCC
- 150,000-200,000

Cirrhosis
- 1.5

Death
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

International study of NAFLD (N=619) diagnosed between 1975-2005
- All liver biopsies centrally ready
- Median follow-up 12.6 yrs
- 193 who died or had OLT
  - 74 (38.3%) of CV disease
  - 36 (18.7%) of non-liver CA
  - 18 (9.3%) of liver complication

### Univariate survival analyses

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


• 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
  – Absolute Risk for NAFLD-HCC: 3-6% over 8.2-21 years
  – NAFLD-HCC Mortality: 0.25%-2.3% over 8.3-13.7%
• 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 cases from SEER (2004–2009)
- Cohort included n =4979 HCC and 14,937 non-HCC matched controls
- Number of HCC cases increased between 2004-2009

Causes of chronic liver disease in HCC

- HCV (55%)
- HBV (9%)
- Alcoholic LD (16%)
- Autoimmune hepatitis/biliary cirrhosis (5%)
- NAFLD (14%)

Independent factors associated with HCC

<table>
<thead>
<tr>
<th>Cause</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>3.68 (3.29-4.11)</td>
</tr>
<tr>
<td>NBNW</td>
<td>1.59 (1.39-1.83)</td>
</tr>
<tr>
<td>HCV</td>
<td>67.93 (58.76-78.53)</td>
</tr>
<tr>
<td>HBV</td>
<td>42.03 (32.63-54.13)</td>
</tr>
<tr>
<td>Autoimmune LD</td>
<td>17.78 (13.55-23.34)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>3.29 (2.86-3.78)</td>
</tr>
</tbody>
</table>

Independent factors associated with 1-year mortality

- Fewer HCV/HBV pts died within 1-year of dx vs NAFLD ( 53% vs. 61%, p<0.05)

Adjusted survival curve by liver disease

- Cox proportional hazard model

• 1500 Veterans Affairs 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)
  – ~13% of patients with HCC in the VA system do not have cirrhosis.
  – NAFLD [OR: 5.4; 95% CI (3.4–8.5)] and MS [OR: 5.0; 95% CI (3.1–7.8)] are main risk factors for HCC in the absence of cirrhosis

Mittal A. Clinical Gastroenterology and Hepatology. 2015.
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

NAFLD is Associated with Impairment of HRQOL and Economic Burden

Patients with NAFLD from NHANES 2001-2011 (N=3,333)

Medicare Beneficiaries who Sought Outpatient Care for NAFLD (2005-2010)

- N
- Male (%)
- Race
- CVD
- DM
- HLD
- HTN
- Charges$
- Pmt ($)

P value reported by t test

Younossi Z et al. AASLD 2015

Younossi Z et al. JCG 2013

NAFLD is associated with tremendous clinical, economic and quality of life burden to patients and society

- This is underestimates (no inpatients and indirect costs)
- The prevalence and cost of NAFLD are growing
Clinical and Routine Labs
• Not very Helpful

Liver Biopsy & Pathologic Protocols

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

Diagnostic & Prognostic Biomarkers for NASH

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

Clinical Predictive Panels
• 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
Treatment of Non-alcoholic Fatty Liver Disease

### Regimens Used to Treat NAFLD/NASH

- Life style modification and weight loss
- Weight loss medications
- Lipid Lowering agents (statins, fibrates)
- 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

### AASLD, ACG, AGA NAFLD Guideline

#### Weight loss and Life Style Modification

- Weight loss reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity. (Strength –1, Evidence- A)
  - Loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation (Strength – 1, Evidence - B)
- Exercise alone in NAFLD may reduce hepatic steatosis but its ability to improve other aspects of liver histology remains unknown (Strength – 1, Evidence - B)

#### Medical Regimens:

- Vitamin E 800 IU/day improves liver histology in non-diabetic with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population. (Strength -1, Quality - B)
## Treatment of NAFLD

### Experimental Regimens Under Consideration

<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>
FLINT Phase 2 Trial Design

The Farnesoid X Receptor Ligand Obeticholic Acid (OCA) in NASH Treatment

- Semisynthetic BA analog 100x more potent than chenodeoxycholic acid in binding FXR
- Improved insulin sensitivity and deductions in markers of liver inflammation and fibrosis

Interim Analysis when 50% of patients completed treatment and had an end-of-treatment liver biopsy

Primary endpoint: Histological improvement defined as:
- No worsening in fibrosis and
- Decrease in NAS of ≥ 2 points

FLINT Study: Improved Liver Histology After 72 Weeks of Treatment

<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>0.08</td>
</tr>
</tbody>
</table>

Lipid Parameters Measured

(*p<0.05, all p-values compared to placebo)

<table>
<thead>
<tr>
<th>Lipid Parameters</th>
<th>Total cholesterol</th>
<th>LDL</th>
<th>HDL</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OCA</td>
<td>Placebo</td>
<td>OCA</td>
<td>Placebo</td>
</tr>
<tr>
<td>Baseline</td>
<td>190</td>
<td>197</td>
<td>112</td>
<td>111</td>
</tr>
<tr>
<td>Δ Base-72 wks (n=240)</td>
<td>+6*</td>
<td>-7*</td>
<td>+9*</td>
<td>-8*</td>
</tr>
<tr>
<td>Δ Base-96 wks (n=240)</td>
<td>-12</td>
<td>-8</td>
<td>-12</td>
<td>-12</td>
</tr>
</tbody>
</table>

NAFLD and NASH: Clinical Update Summary

- NAFLD has tremendous clinical, economic and PRO 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
- Currently, there are very few effective treatment options for NASH
- Development of effective treatment regimens tested in well-designed studies with adequate sample size, long duration of treatment, robust endpoints and accompanying biomarkers are urgently needed
NAFLD/NASH

Audience Questions
Concluding Remarks

Michael Trauner, MD
Professor of Medicine
Chair, Division of Gastroenterology and Hepatology
Medical University of Vienna
Vienna, Austria
PBC - Summary

- PBC is a heterogeneous disease with variable individual clinical outcomes
- Significant proportion of patients with PBC has insufficient response to available UDCA treatment
  - Multiple factors involved
  - Risk of disease progression
  - Biochemical response-guided therapy (Fibroscan?)
- Novel therapies (beyond UDCA) have evolved
  - Obeticholic acid
  - Fibrates
  - Nor-UDCA
  - Novel immunologic approaches (e.g., rituximab)

Abbreviations: PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.
NASH - Summary

• Underappreciated liver disease that can progress to cirrhosis, HCC, and need for transplantation

• Noninvasive methods to predict prognosis, track progression, and measure therapeutic efficacy are urgently needed
  – Fibrosis stage as most important prognostic factor

• Treatment of metabolic comorbidities may have beneficial impact on liver disease

• Novel therapies beyond lifestyle modification are urgently needed and have evolved
  – Obeticholic acid, aramchol, GFT505, cenicriviroc, simtuzumab

Abbreviations: HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis.
Thank You!

For the most current information and clinically meaningful education on chronic liver diseases, please visit www.ChronicLiverDisease.org