Recent Advances in Primary Biliary Cirrhosis
Disease Pathways and Potential Targets of Therapy

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The Netherlands
Primary Biliary Cirrhosis

Characteristics

Sex (f:m) 9 : 1
Age 40 - 60
Survival without treatm. 7.5-16 years
Cholestatic enzyme pattern
Autoantibodies

AP, γGT ↑

AMA (anti-PDC-E2)

Symptoms:
• Fatigue
• Itch
• “Dry eye, dry mouth”
• ...

Courtesy of Ulrich H. W. Beuers, MD.
Primary Biliary Cirrhosis

**Pathogenesis**

- Immune-mediated bile duct injury
- Aggravation of bile duct injury by hydrophobic bile acids
- Cholestasis with retention of hydrophobic bile acids in liver
- Liver cell damage, apoptosis, necrosis, fibrosis, cirrhosis

Liver failure

Primary Biliary Cirrhosis
- Pathogenesis -

- Genetic predisposition
- Exogenous factors
- Endogenous factors
Primary Biliary Cirrhosis
- Pathogenesis -

• Genetic predisposition
  Family members:  6% PBC
  GWAS*: HLA-DQ-B1, II12A, II12B2, STAT4,…

• Exogenous factors

• Endogenous factors

*GWAS: Genome-wide association study.
Primary Biliary Cirrhosis
- Pathogenesis -

• Genetic predisposition

• Exogenous factors

• Endogenous factors
Sequence Homology of the Human Pyruvate Dehydrogenase Complex (PDC-E2\textsubscript{208-237}) with Bacterial Proteins

Inner lipoyl domain of the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2)

Model of AMA Formation and Cholangiocyte Damage in Primary Biliary Cirrhosis

IgA AMA transfer via cholangiocytes

With permission from Rieger R, Gershwin ME. J Autoimmun. 2007;28:76-84.
Primary Biliary Cirrhosis

- Pathogenesis -

- Genetic predisposition

- Exogenous factors

- Endogenous factors
Primary Biliary Cirrhosis

Characteristics

Sex (f:m) 9 : 1
Age 40 - 60
Survival without treatment 7.5-16 years

Cholestatic enzyme Pattern

Autoantibodies
AMA (anti-PDC-E2)

Too low HCO$_3^-$?


Signs & symptoms:
- Fatigue
- Itch
- “Dry eye, dry mouth”
- ...

Courtesy of Ulrich H.W. Beuers, MD.
Bile Formation in Mice and Men

Source of bile

<table>
<thead>
<tr>
<th>Species</th>
<th>Source of Bile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>100% Hepatocytes</td>
</tr>
<tr>
<td>Human</td>
<td>50% Cholangiocytes, 50% Hepatocytes</td>
</tr>
</tbody>
</table>


Bile Formation in Mice and Men

Source of bile

<table>
<thead>
<tr>
<th>Species</th>
<th>Hepatocytes</th>
<th>Cholangiocytes (HCO₃⁻)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Human</td>
<td>80%</td>
<td>20%</td>
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</table>

Bile salt composition

<table>
<thead>
<tr>
<th>Species</th>
<th>Glycine conjugates</th>
<th>Taurine conjugates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>pKₐ &gt; 4</td>
<td>pKₐ 1-2</td>
</tr>
<tr>
<td>Human</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Glycochenodeoxycholic acid induces mucosal injury in mouse gastric mucosa at pH 1 and 3, but not pH 5

Slide courtesy of Dr. Ulrich Beuers.
Bile Acids, but Not Bile Salts, Invade Cholangiocytes at Low pH

Calculated protonation rate of bile salts

GCDCA in human H69 cholangiocytes

Top graphic courtesy of Dr. Ulrich Beuers.
The Cholangiocyte Secretes HCO$_3^-$ Upon Various Stimuli

Hypothesis: The Biliary $\text{HCO}_3^-$ Umbrella

CDCA

Bile

Apoptosis

Fibrosing cholangiopathy

Cholangiocyte

CAMP

ACh

Secretin

M3R


Defect of the Biliary HCO$_3^-$ Umbrella in PBC?

PDC-E2-like Peptides are Aberrantly Expressed on Apoptotic and Senescent Cholangiocytes

Primary Biliary Cirrhosis

Pathogenesis

- Immune-mediated bile duct injury
- Aggravation of bile duct injury by hydrophobic bile acids
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- Liver cell damage, apoptosis, necrosis, fibrosis, cirrhosis
- Liver failure

Primary Biliary Cirrhosis: Therapy

**Pathogenesis**

1. Immune-mediated bile duct injury
2. Aggravation of bile duct injury by hydrophobic bile acids
3. Cholestasis with retention of hydrophobic bile acids in liver
4. Liver cell damage, apoptosis, necrosis, fibrosis, cirrhosis

Liver failure

Ursodeoxycholic acid (13-15 mg/kg/d)

Effect of UDCA on Survival in PBC

“Paris I Criteria”

- Bilirubin: ≤1 mg/dL
- ALP: ≤3 x ULN
- AST: ≤2 x ULN

- 10-year survival without transplantation, according to 1-year biochemical response to UDCA:
  - Responders (n=179): 90% (95% CI: 81% to 95%)
  - Nonresponders (n=113): 51% (95% CI: 38% to 64%)
  - $p<0.0001$; RR, 0.4; 95% CI: 0.3-0.5

Stimulation of hepatocellular secretion

Biliary HCO$_3^-$ umbrella

Stimulation of cholangiocellular secretion

Bile acids

Apoptosis

Necrosis

Antiapoptotic effects

Reduction of bile toxicity

Potential Mechanisms and Sites of Action of UDCA in Cholestatic Liver Diseases

UDCA Stimulates Impaired HCO$_3^-$ Secretion in PBC

- UDCA
- Bile
- Apoptosis
- Senescence
- Fibrosing cholangiopathy

- CDC A
- CDCA
- UDCA
- P2Y
- ATP
- TGR-5
- ACh
- Secretin
- M3R
- SR
- CDCA
- HCO$_3^-$
- Cl$^-$
- H$_2$CO$_3$
- Ca$^{++}$
- InsP$_3$
- ER
- CA
- ATP
- CO$_2$
- H$_2$O
- cAMP

Reference:
Primary Biliary Cirrhosis:

Pathogenesis

- Immune-mediated bile duct injury
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Ursodeoxycholic acid (13-15 mg/kg/d)

Liver failure

Liver transplantation

Primary Biliary Cirrhosis: *Future* Therapy

**Pathogenesis**

- Immune-mediated bile duct injury
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Liver failure

- Ursodeoxycholic acid (13-15 mg/kg/d)
- Liver transplantation

*RCT* (Phase 3)

Budesonide?

Combined UDCA and Glucocorticoids Upregulate an Alternate AE2 Promoter in Human Liver Cells

UDCA + Glucocorticoid

Primary Biliary Cirrhosis: *Future* Therapy

**Pathogenesis**

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**Liver failure**

- Ursodeoxycholic acid (13-15 mg/kg/d)
- Budesonide?
- norUDCA?

**RCT (Phase 3)**

NorUDCA is a Potent HCO$_3^-$ Secretagogue in Man and Rodents

HCO$_3^-$ - Cl$^-$ - Cl$^-$ - Cl$^-$ - Cl$^-$ - Cl$^-$

Secretin

ACh

ATP

P2Y

AE2

Cl$^-$

HCO$_3^-$

H$_2$CO$_3$

HCO$_3^-$

H$_2$O + CO$_2$

cAMP

ER

M3R

ACh

CDCA

HCO$_3^-$

OH

HO

COOH

TGR-5

norUDCA

Bile

Apoptosis

Senescence

Fibrosing cholangiopathy

Primary Biliary Cirrhosis: Future Therapy

**Pathogenesis**

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Ursodeoxycholic acid (13-15 mg/kg/d)

RCT (Phase 3)

- Budesonide?
- norUDCA?
- Nuclear receptor agonists?
  - FXR: obeticholic acid?

Liver transplantation

The Farnesoid X Receptor (FXR) Protects Against Toxic Effects of Hydrophobic Bile Acids


Slide courtesy of Dr. Ulrich Beuers.
The Farnesoid X Receptor (FXR) Protects Against Toxic Effects of Hydrophobic Bile Acids


Slide courtesy of Dr. Ulrich Beuers.
The Farnesoid X Receptor (FXR) Protects Against Toxic Effects of Hydrophobic Bile Acids

For details, see:
Baghdasaryan A, et al. 

Slide courtesy of Dr. Ulrich Beuers.
FXR Agonists Stimulate Biliary HCO$_3^-$ Secretion in Rodents

Primary Biliary Cirrhosis: Future Therapy

Pathogenesis

Immune-mediated bile duct injury

Aggravation of bile duct injury by hydrophobic bile acids

Cholestasis with retention of hydrophobic bile acids in liver

Liver cell damage, apoptosis, necrosis, fibrosis, cirrhosis

Liver failure

Ursodeoxycholic acid (13-15 mg/kg/d)

Budesonide? norUDCA?

RCT (Phase 3)

Nuclear receptor agonists?
- FXR: obeticholic acid?
- PPARα: beza-, fenofibrate?

RCT (Phase 3)

Liver transplantation

FXR Agonists Stimulate Biliary HCO₃⁻ Secretion in Rodents

Primary Biliary Cirrhosis: *Future* Therapy

**Pathogenesis**

- Immune-mediated bile duct injury
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**Ursodeoxycholic acid (13-15 mg/kg/d)**

- Budesonide?
- norUDCA?
- Nuclear receptor agonists? - FXR: obeticholic acid? - PPARα: beze-, fenofibrate?

**Liver failure**

- Liver transplantation

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- ...

Courtesy of Ulrich H.W. Beuers, MD.
Identification of a Neuronal Activator in Serum of Pruritic Patients

- Molecular size: <3 kD
- No peptide
- G-protein coupled receptor
- Amphiphilic upon protonation: hydrophobicity ↑

Lysophosphatidic acid (LPA)

Lysophosphatidic Acid (LPA) is Formed by Autotaxin in Serum

Increased Autotaxin (ATX) Activity is Specific for Pruritus of Cholestasis

*P <.05. ***P <.001 (ANOVA).

Autotaxin Activity Mirrors Therapeutic Efficacy in Pruritus of Cholestasis

Abbreviations: ATX, autotaxin; MARS, molecular absorbance recirculating system.
Potential Pruritogens in Cholestasis

Pruritogens...

- Accumulate in the systemic circulation
- Are (biotrans-)formed in the liver and/or gut
- Affect the endogenous serotonergic and opioidergic system
- Autotaxin \rightarrow LPA
- Are secreted into bile

Slide courtesy of Dr. Ulrich Beuers.
Pathogenesis of Pruritus in Cholestasis

**Targets for Interventional Therapies: Summary**

Pruritogens...

- Accumulate in the systemic circulation
- Are (biotrans-)formed in the liver and/or gut
- Are secreted into bile
- Nasobiliary drainage
- Cholestyramine

**Autotaxin → LPA**

**Targets for Interventional Therapies**

- Naltrexone
- Sertraline
- Rifampicin

Pathogenesis of Pruritus in Cholestasis

Autotaxin is formed in the liver and/or gut. It is (biotrans-)formed in the systemic circulation and secreted into bile. Pruritogens such as Naltrexone, Sertraline, and Rifampicin affect the endogenous serotonergic and opioidergic system. Rifampicin is a target for interventional therapies.


Slide courtesy of Dr. Ulrich Beuers.
Challenges and New Opportunities in the Clinical Management of PBC

David E.J. Jones, MD, PhD
Dean of Research and Innovation
Newcastle University
Newcastle upon Tyne, United Kingdom
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

Abbreviations: PBC, primary biliary cirrhosis.
Suboptimal Therapy in PBC—What Are the Potential Causes?

- In UK-PBC national cohort, 20% of PBC patients are not treated with ursodeoxycholic 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

Abbreviations: PBC, primary biliary cirrhosis.
UDCA Is an Effective Therapy in PBC

Abbreviations: PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.
### Criteria for “Response” to UDCA in PBC

#### Paris Criteria
- Bilirubin ≤1 mg/dL + AST ≤2 x ULN + ALP ≤3 x ULN after 12/12 UDCA at 13-15 mg/kg
- **Responder:** 96% survival vs 99% control population at 5 years
- **Nonresponder:** 69% survival vs 68% Mayo Predicted Survival

#### Barcelona Criteria
- ALP decrease by 40% or normalized After 12/12 UDCA at 13-15 mg/kg

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

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

Criteria for “Response” to UDCA in PBC

Early-Stage Patients

- Early stage defined as normal albumin and bilirubin
- Paris II criteria: ALT and ALP $\leq 1.5 \times$ ULN after medical therapy

$P = NS$ for Barcelona, Paris I, Rotterdam, and Toronto; $P < .05$ for Paris II.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; NS, not significant; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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.
Factors Predicting Outcome in PBC in the UK-PBC Patient Cohort

Cox Proportionate Hazards Model: Time-to-Event Analysis

### 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 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>
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<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>
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<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>
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<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>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 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>
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<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>
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<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>
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<tr>
<td>12 months 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>

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; LN, natural log; PBC, primary biliary cirrhosis; SE, standard error.
Just How Effective Is UDCA in PBC?

*The Conventional Model*

- 79.7% of UDCA-treated patients are UDCA-responsive (Paris I)
- 797 beneficiaries per 1000 patients in UK-PBC cohort
- UDCA is highly effective!

*BUT*

- Significant proportion of patients meet response criteria before therapy is commenced

Abbreviations: PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.
Just How Effective Is UDCA in PBC?

1000 patients

80% → 800 UDCA-treated

20% → 200 UDCA-untreated

80% → 640 responders

20% → 160 nonresponders

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

Abbreviations: PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.
Slide courtesy of David Jones, MD.
>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.

Abbreviation: UDCA, ursodeoxycholic acid.
Potential Mechanisms for UDCA Nonresponse 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)

Abbreviations: PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.
Drugs Under Evaluation for 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)

Abbreviations: FXR, farnesoid X receptor; PBC, primary biliary cirrhosis; PPAR, peroxisome proliferator-activated receptor.
Biochemical Effects of Rituximab in Patients with PBC and an Incomplete Response to UDCA

- Open-label study of rituximab treatment in patients with PBC and incomplete responses to UDCA (n = 6)
- Rituximab was well tolerated and associated with reductions in serum immunoglobulins (IgA; IgM) and antimitochondrial antibodies
- Significant reductions in serum ALP levels were observed up to 36 weeks following rituximab treatment

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

Abbreviations: ALP, alkaline phosphatase; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.
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?

Abbreviations: FCF-19, fibroblast growth factor 19; FXR, farnesoid X receptor; GI, gastrointestinal; PBC, primary biliary cirrhosis; UDCA, ursodeoxycholic acid.
FXR-Agonism as a Therapeutic Option in PBC—Obeticholic Acid (INT-747)  
Phase II Data in PBC Patients on Stable UDCA

*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. With permission from Mason AL, et al. Hepatology. 2010:52(suppl S1):357A.
FXR-Agonism as a Therapeutic Option in PBC—Obeticholic Acid (INT-747)

Phase II Data

Patients Withdrawing Due to Pruritus (%)

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

With permission from Mason AL, et al. Hepatology. 2010:52(suppl S1):357A.
FXR-Agonism as a Therapeutic Option in PBC—Obeticholic Acid (INT-747) 
*Phase III (POISE)*

**N = 216**

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

- **Positive Response**
  - ALP $< 1.67 \times \text{ULN}$ and bilirubin WNL, and $\geq 15\%$ ALP reduction

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 \(\text{ALP} < 1.67 \times \text{ULN} \) with bilirubin \(\leq \text{ULN}\) and \(\geq 15\%\) 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)*

**Graph:**
- **Y-axis:** LS Mean (SE) Δ in ALP (U/L) from Baseline
- **X-axis:** Time (months)
- **Legend:**
  - Placebo (n=73)
  - Titrated OCA (n=70)
  - 10 mg OCA (n=73)

- **Statistical Significance:**
  - 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)*

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

*LS Mean (SE) Δ in ALT (U/L) from baseline*

*Time (months)  
0  6  12*

*P <.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)

*P < .05 vs placebo.
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.  
Pruritus Visual Analog Scale Score

* $p<0.05$ vs placebo for LS mean change

VAS score range: 0 = no pruritus, 100 = severe pruritus
FXR-Agonism as a Therapeutic Option in PBC—Obeticholic Acid (INT-747)  
*Phase III Data (POISE)*

![Graph showing mean (SE) LDL cholesterol levels over time for Placebo (n=73), Titrated OCA (n=70), and 10 mg OCA (n=73).](image)

Abbreviations: FXR, farnesoid X receptor; OCA, obeticholic acid; LDL, low density lipoprotein; 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; HDL, high density lipoprotein; OCA, obeticholic acid; PBC, primary biliary cirrhosis; SE, standard error.

Clinician Awareness Is a Challenge for Effective Therapy in PBC

Competence: “Highly Competent”

Early Diagnosis/Treatment

Heps: 80%
Gastros: 65%

Practice Performance: “Always/Often”

Early Diagnosis

Heps: 88%
Gastros: 87%

Early Treatment

Heps: 76%
Gastros: 65%

Abbreviations: gastro, gastroenterologist; hep, hepatologist; PBC, primary biliary cirrhosis


Slide courtesy of David E. J. Jones, MD, PhD.
Clinician Competence in and Use of Response Criteria for Assessing Treatment Response in PBC

Competence: "Highly Competent"

Practice Performance: "Always/Often"

Responders (%)

<table>
<thead>
<tr>
<th></th>
<th>Heps</th>
<th>Gastros</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heps</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>Gastros</td>
<td>76</td>
<td>42</td>
</tr>
</tbody>
</table>

Abbreviations: gastro, gastroenterologist; hep, hepatologist; PBC, primary biliary cirrhosis
Slide courtesy of David E. J. Jones, MD, PhD.
Effect of Untreated or Suboptimally Treated PBC on Disease Progression/Mortality

Competence: “Highly Competent”

<table>
<thead>
<tr>
<th></th>
<th>Responders (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heps</td>
<td>80</td>
</tr>
<tr>
<td>Gastros</td>
<td>60</td>
</tr>
<tr>
<td>Heps</td>
<td>80</td>
</tr>
<tr>
<td>Gastros</td>
<td>40</td>
</tr>
</tbody>
</table>

Effect on Disease Progression

Causes of Suboptimal Treatment

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

- 35% of primary biliary cirrhosis (PBC) patients report perceived QOL impairment vs 6% of healthy controls ($P < .0001$)

- 46% of PBC patients rated their perceived health status as fair or poor vs 15% of healthy controls ($P < .0001$)

- In terms of change over time, 49% of PBC patients reported their health as worse compared with the previous year vs 14% of healthy controls ($P < .0001$)

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

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

- Fatigue is important symptom with significant impact on patient
  - Fatigue had its greatest impact on perceived QOL when accompanied by symptoms of social dysfunction
  - 89% of patients with severe fatigue and poor QOL had symptoms of impaired social function compared with 11% of patients with severe fatigue and no QOL impairment ($P < .0001$)

- Critical issue is how patients adapt and cope with fatigue as this will ultimately affect impact of fatigue on QOL

- Disease management should ultimately target both the underlying biology of the disease as well as symptoms

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