New therapies for CBP and CEP

Christopher L. Bowlus, MD
Lena Valente Professor and Chief
Division of Gastroenterology and Hepatology
Disclosures

• Grants
  • Allergan, BMS, Cymabay, Gilead, GSK, Intercept, Novartis, NGM, Shire, Takeda

• Consulting
  • Cymabay, Eli Lilly, GSK, Patara, Parvus, Pliant
Trends in Liver Transplant for Autoimmune Liver Diseases in the USA

http://optn.transplant.hrsa.gov/latestData/rptData.asp
Accessed May 2, 2019
Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases

Keith D. Lindor, Christopher L. Bowlus, James Boyer, Cynthia Levy, and Marlyn Mayo
PBC Diagnostic process

- Diagnostic criteria: must have 2 of 3
  - ALP > 1.5 times ULN for > 24 weeks
  - Serum AMA > 1:40 (or PBC specific ANA, i.e. GP210 or SP100)
  - Liver biopsy showing nonsuppurative cholangitis and bile duct injury

Abbreviations: ALP, alkaline phosphatase; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; PBC, primary biliary cholangitis; ULN, upper limit of normal.
PBC Diagnostic Algorithm

Abbreviations: ALP, alkaline phosphatase; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; PBC, primary biliary cholangitis; ULN, upper limit of normal.

PBC Variant Syndromes

AMA-negative PBC
- 50% will have ANA\textsuperscript{[a]}
- PBC-specific ANA: anti-gp210, anti-sp100\textsuperscript{[b]}
- Same clinical presentation; may have reduced survival\textsuperscript{[c,d]}

Overlap syndrome with AIH\textsuperscript{[b]}
- “Paris criteria” requires 2 of 3
  - 1) ALT > 5 X ULN; 2) IgG > 2 X ULN or ASMA; 3) moderate to severe interface hepatitis

Ductopenic variant
- Rapid onset of ductopenia, severe icteric cholestasis, rapid progression towards cirrhosis \textsuperscript{[b]}

Gastroenterology 2010;139(5):1481

Bile Acid Targets

1. Tolerance is broken

2. Apoptotic blebs

3. Immune complex

4. Expansion of autoreactive immune cells target BEC

5. Inflammation, cholestasis and fibrosis

Abatacept

Rituximab

Ustekinumab

Baricitinib

Cytokines
Lack of Complete Biochemical Response Predicts Disease Progression

PBC: Biochemical Response to Urso at 1 Year

Incomplete Responders are more likely to be:
- Younger Women
- Men
- Hispanic

Elevated ALP and Bilirubin Values Are Associated with Higher Risk for Liver Transplant/Death

*Estimated with cubic spline function.
# GLOBE Score Online Calculation

The GLOBE score for patients with Primary Biliary Cholangitis (PBC)

The GLOBE score is an internationally relevant and validated risk assessment tool, able to accurately stratify PBC patients to high and low risk.

<table>
<thead>
<tr>
<th>Age, years at initiation of UDCA therapy</th>
<th>53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin level, µmol/L or mg/dl after one year of UDCA therapy</td>
<td>1.0</td>
</tr>
<tr>
<td>Alkaline phosphatase level, U/L after one year of UDCA therapy</td>
<td>232</td>
</tr>
<tr>
<td>Albumin, g/L after one year of UDCA therapy</td>
<td>37</td>
</tr>
<tr>
<td>Platelets, x 10^9/L after one year of UDCA therapy</td>
<td>210</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GLOBE score:</th>
<th>0.62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold:</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Is the transplant-free survival diminished when comparing with an age- and sex-matched population? **YES**

Liver transplant-free survival

<table>
<thead>
<tr>
<th>GLOBE score</th>
<th>mean survival of age- and sex-matched patients in age group 52-58 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year</td>
<td>93.6%</td>
</tr>
<tr>
<td>5-year</td>
<td>88.8%</td>
</tr>
<tr>
<td>10-year</td>
<td>72.7%</td>
</tr>
<tr>
<td>15-year</td>
<td>56.4%</td>
</tr>
</tbody>
</table>

Interpretation of the GLOBE score:
## GLOBE Score Online Calculation

### The GLOBE score for patients with Primary Biliary Cholangitis (PBC)

The GLOBE score is an internationally relevant and validated risk assessment tool, able to accurately stratify PBC patients to high and low risk.

<table>
<thead>
<tr>
<th>Age, years at initiation of UDCA therapy</th>
<th>63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin level, μmol/L or mg/dl after one year of UDCA therapy</td>
<td>0.7</td>
</tr>
<tr>
<td>Alkaline phosphatase level, U/L after one year of UDCA therapy</td>
<td>143</td>
</tr>
<tr>
<td>Albumin, g/L after one year of UDCA therapy</td>
<td>37</td>
</tr>
<tr>
<td>Platelets, x 10^9/L after one year of UDCA therapy</td>
<td>210</td>
</tr>
</tbody>
</table>

**GLOBE score:** 0.57

**Threshold:** 1.01

**Is the transplant-free survival diminished when comparing with an age- and sex-matched population?**

**NO**

**Liver transplant-free survival**

<table>
<thead>
<tr>
<th>GLOBE score</th>
<th>mean survival of age- and sex-matched patients in age group 58-66 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year</td>
<td>93.9%</td>
</tr>
<tr>
<td>5-year</td>
<td>98.2%</td>
</tr>
<tr>
<td>10-year</td>
<td>96.1%</td>
</tr>
<tr>
<td>15-year</td>
<td>89.0%</td>
</tr>
</tbody>
</table>

Marilixibat
POISE Study - Obeticholic acid (OCA)

- 12 month double blind study followed by long term safety extension
- Response defined as
  - ALP < 1.67 X ULN
  - > 15% reduction in ALP
  - Total bilirubin < ULN
- Pruritus was the most common adverse effect

Majority of Patients had Improvement or No Worsening in Fibrosis Stage after 3 Years of OCA Treatment

F0=no fibrosis; F1=periportal fibrosis; F2=bridging fibrosis with rare septa; F3=bridging fibrosis with many septa; F4=incomplete cirrhosis; F5=cirrhosis

Warning for Decompensated Cirrhosis

OCALIVA® (obeticholic acid) tablets, for oral use
Initial U.S. Approval: 2016

WARNING: HEPATIC DECOMPENSATION AND FAILURE IN INCORRECTLY DOSED PBC PATIENTS WITH CHILD-PUGH CLASS B OR C OR DECOMPENSATED CIRRHOSIS
See full prescribing information for complete boxed warning

- In postmarketing reports, hepatic decompensation and failure, in some cases fatal, have been reported in patients with primary biliary cholangitis (PBC) with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when OCALIVA was dosed more frequently than recommended. (5.1)
- The recommended starting dosage of OCALIVA is 5 mg once weekly for patients with Child-Pugh Class B or C hepatic impairment or a prior decompensation event. (2.2)
Fibrates and other PPAR Agonists

- 3 isoforms PPARs
  - $\alpha$, $\gamma$, $\delta$
- Regulatory role on bile acids
- Modulate glucose and lipid metabolism, and energy homeostasis
- Reduce cytokine production by intrahepatic macrophages
- Reduce fibrogenic capacity of hepatic stellate cells

- Bezafibrate (Pan-PPAR agonist)
- Fenofibrate (PPAR$\alpha$ agonist)
- Seladelpar (PPAR$\delta$ agonist)
- Elafibranor (PPAR$\alpha$/\$\delta$ agonist)
BEZURSO - Bezafrirate

- 24 month double blind study
- Response defined as
  - Normalization of ALP, total bilirubin, AST, INR
- Entry ALP lower than POISE
Bezafibrate safety

- **Transaminases > 5 xULN:**
  - 1 under placebo
  - 3 under bezafibrate, treatment discontinuation in 2, resolved in all
- **CPK > 5 xULN:**
  - 1 under bezafibrate (statin not discontinued), resolved after discontinuation
- **Serum creatinine:**
  - +5% under bezafibrate vs. -3% under placebo at M24 (p<.01)
  - Median (IQR) at M24 (µmole/L): 65.5 (58 – 71) vs. 61.0 (55 – 70)
Bezafibrate and OCA in patients with PBC

- 16 patients from the POISE* study who received OCA (5 or 10 mg QD) ± UCDA for 4–5 years
  - OCA terminated in 3 patients (pruritus n=2)

- After 5 years, bezafibrate 400 mg QD added to OCA + UCDA in 11 patients
  - 9 female; mean age 64 years; mean FibroScan 9.3 kPa (range 4.3–21.8)
  - Bezafibrate terminated in 1 patient due to myalgia

*PBC OCA International Study of Efficacy; †P-values calculated by per-protocol analysis.
Seladelpar Phase 2 Study in PBC

Decreases in AP >45% observed at 5/10 mg and 10 mg

Dose adjustment for 5/10 mg group

Mean Percent AP Change

Week

Mean % Change

Dose adjustment for 5/10 mg group

P<0.0001 for both groups compared to baseline values

Mean ± SEM

Bowlus CL. et al. Hepatology 2018; LB-03.
Elafibranor Phase 2 Study in PBC

Patients with PBC
- Non-cirrhotic
- Inadequate UDCA response

Primary endpoint
% ALP change

UDCA continued in all patients

80 mg -48%
120 mg -41%

A retrospective, multicenter, international cohort study of patients who underwent LT for PBC over the past 30 years

- Factors associated with PBC recurrence and long-term outcomes analyzed
- Total of 941 patients analyzed
  - 211 (22%) received preventative UDCA
    - 10–15 mg/kg/QD from Week 2 post-LT
- Mean follow-up: 9.7 ± 7.7 years
  - 264 PBC recurrences
  - 111 graft losses
  - 298 deaths

Corpechot C. et al. *J Hepatology* 2019;70:e84
PBC Treatment Summary

Urso at 15 mg/kg/d

Complete Response
• ALP < 200 AND
• Total Bilirubin < 1.0

Incomplete Response
Urso Intolerant
Advanced Disease

Obeticholic Acid
• Not decompensated cirrhosis

Fenofibrate/Bezafibrate (*Off-Label*)
• Intolerant to OCA
• Not interested in clinical trials

Clinical Trials
Primary Sclerosing Cholangitis (PSC)

- Inflammatory/fibrotic disease of the large bile ducts
- Associated with colitis
- Male predominance
- Affects wide age range
Even if no symptoms, perform a colonoscopy
PSC Diagnosis

Large Duct PSC (Classic Form)
• Typical segmental strictures on cholangiogram
• Absence of secondary causes
• With or without IBD

PSC/AIH Overlap
• No consensus on criteria or treatment
• AIH transition to PSC vs concomitant diseases

Small Duct PSC
• Normal cholangiogram
• Typical sclerosing cholangitis histology
• Absence of IBD requires exclusion of genetic cause of cholestasis
Transplant-Free Survival in PSC

![Graph showing Transplant-Free Survival in PSC with data points from 1987 to 2017, comparing Liver Tx Centers and Non-Liver Tx Centers with the IPSCSG.]

- Median Survival (Y) for Liver Tx Centers and Non-Liver Tx Centers with data points from 1987 to 2017.
- Year of Publication on the x-axis, ranging from 1987 to 2017.
- Median Survival values for each year are represented by bars, with Liver Tx Centers in grey, Non-Liver Tx Centers in blue, and IPSCSG in orange.
Transplant-Free Survival in PSC Partners Registry

811 self-identified PSC Patients
- 65.1% confirmed diagnosis
- Mean age 41.7 ± 15.5 years
- Mean age at diagnosis 32.4 ± 14.5 years
- 67.1% with IBD

Median transplant-free survival 21 years
- 95% CI 17.2 – 24.8 years

Causes of Mortality in PSC

- Transplants
- Liver-related Deaths
- PSC-related Cancer Deaths
- Other Deaths
Cancers in PSC

**Cholangiocarcinoma**
- Prevalence = 4.8% to 36.4%
- 38% to 50% diagnosed in first year
- Annual incidence = 0.6% to 1.5%
- Relative Risk = 160 to 1560

**Gallbladder Cancer**
- Prevalence = 0.9% to 14%
- High rate of dysplastic polyps

**Colon Cancer**
- 6% to 20% at 20-years
- 5 to 10 fold increase risk compared to UC without PSC
- Tend to be right-sided
- Earlier age than IBD alone
Surveillance for Hepatobiliary Cancer in PSC

- Imaging +/- CA19-9 every 6-12 months
- Dominant stricture, worsening cholestasis, or rising CA19-9
  - ERCP
- Gallbladder polyp
  - < 8mm – monitor
  - > 8mm – consider cholecystectomy
- Surveillance not required in
  - Age < 20 years
  - Small duct PSC
## PSC PROGNOSTIC MODELS

<table>
<thead>
<tr>
<th></th>
<th>King’s ((n = 126))</th>
<th>Hannover ((n = 273))</th>
<th>Sweden ((n = 305))</th>
<th>Europe(^3) ((n = 330))</th>
<th>Revised Mayo ((n = 405; 124))</th>
<th>PREsTo ((n = 509; 278))</th>
<th>Amsterdam Oxford ((n = 692; 264))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variceal Bleeding</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Biopsy Stage</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years from Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

1 Persistently elevated bilirubin; 2 Cases with variceal bleeding (4% of total) excluded; 3Time-dependent model

If Urso works, wouldn’t we know by now?

Didn’t work in the US

Didn’t work in Scandinavia
Nor-Urso Phase 2 Study in PSC

• Double-blind, placebo-controlled trial
• 12 weeks treatment
• 222 pts. screened
  • 159 randomized
  • 126 PP analysis

Obeticholic Acid Phase 2 Study in PSC

Baseline Mean (SD): Placebo: 563 (300); OCA 1.5-3 mg: 423 (123); OCA 5-10 mg: 429 (178)

Cilofexor Phase 2 Study in PSC

NGM 282 Phase 2 Study in PSC

**Mean ALP (U/L)**

- **Baseline**:
  - Placebo (n=20): 356
  - 1 mg (n=21): 383
  - 3 mg (n=21): 354

- **Week 12**: 409

**UDCA use did not impact treatment response at W12**

*p = 0.78*

*p = 0.22*

*p = 0.73*

NGM 282 Phase 2 Study in PSC

Mean Change in ELF Score

- Placebo (n=20)
- 1 mg (n=21)
- 3 mg (n=21)

ELF Score

-0.4
-0.3
-0.2
-0.1
0.0
0.1

p = 0.023
p = 0.049

Vancomycin for Treatment of PSC in Kids

14 pediatric PSC cases; Mean treatment of 54 months

Vancomycin versus Metronidazole in PSC

Vancomycin

Metronidazole

P < 0.05 at each dose

**K. pneumoniae**

- **b**
  - SPF mice
  - HC mice
  - PSCUC mice
  - UC mice
  - (Time post-inoculation (d))

**P. mirabilis**

**E. gallinarum**
International PSC Study Group

- Retrospective outcome analysis of PSC patients diagnosed from 1980 to 2010 at 37 centers in Europe, North America, and Australia
- 7,121 PSC patients; 2,616 died or had a LT; and 721 developed HB malignancy (594 CCA)
Take Home Messages

**Primary Biliary Cholangitis**
1. Liver Biopsy
   1. In cases of AMA negative PBC
   2. If ALT > 5 X ULN
2. Be skeptical of PBC/AIH Overlap
3. Do not settle for incomplete biochemical response with Ursodiol

**Primary Sclerosing Cholangitis**
1. Ursodiol or clinical trial remain only options for treatment of PSC
2. Surveillance for Malignancies
3. High index of suspicion for cholangiocarcinoma
Muchas Gracias!