CLINICAL INSIGHTS INTO THE MANAGEMENT OF PRIMARY BILIARY CHOLANGITIS (PBC)

This activity is supported by an educational grant from Intercept Pharmaceuticals.

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Chronic Liver Disease Foundation
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Educational Objectives

• Define the prevalence, pathophysiology, 4 stages of progression and clinical manifestations of PBC

• Apply clinical and evidence-based diagnostic criteria and prognostic models to evaluate patients for PBC

• Implement clinical and evidence-based individualized PBC treatment plans into clinical practice to improve long term outcomes
Primary Biliary Cholangitis (PBC)
PBC Is a Chronic, Progressive Autoimmune Disease

- Factors possibly associated with onset and perpetuation of bile-duct injury in PBC

*PBC is characterized by destruction of the interlobular and septal bile ducts that may lead to cirrhosis*
## PBC Phenotype

<table>
<thead>
<tr>
<th><strong>Age</strong></th>
<th>Usually &gt;45 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>Female &gt; Male (9:1)</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td>AMA in ~95%; disease-specific ANA in ~30%-50%; ASMA may be present</td>
</tr>
<tr>
<td><strong>Immunoglobulin</strong></td>
<td>IgM typically elevated</td>
</tr>
<tr>
<td><strong>MRCP</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Liver Histology</strong></td>
<td>Lymphocytic infiltrate; inflammatory duct lesion; granuloma may be present</td>
</tr>
<tr>
<td><strong>Coexisting IBD</strong></td>
<td>Not typical</td>
</tr>
</tbody>
</table>

PBC is commonly characterized by slow progression of cholestasis followed by hepatic dysfunction and decompensation.

- Widespread use of AMA testing enabled the diagnosis of PBC patients before they develop symptoms of cholestasis or hepatic decompensation.

## Differential for Cholestatic Liver Biochemistry

- Drug-induced liver injury
- Inherited cholestasis
- Idiopathic ductopenia
- Malignant infiltration
- Nonalcoholic fatty liver disease
- Obstructive biliary lesion
- Primary biliary cholangitis
- Primary sclerosing cholangitis
- Sarcoidosis

## Spectrum of Autoimmune Liver Injuries

- Autoimmune hepatitis
- Primary biliary cholangitis
- Primary sclerosing cholangitis
- IgG4-related disease

Algorithm for the Diagnosis of PBC

US, ultrasound; MRCP, magnetic resonance cholangiopancreatography; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies

Survival Rates, Elastography and PBC

Survival according to baseline LSM

Survival without adverse outcome

Total follow-up (years)

≤ 9.6 kPa

> 9.6 kPa

Abbreviation: LSM, liver stiffness measurement
Higher APRI Is Associated with Lower Transplant-Free/Overall Survival in PBC

Abbreviation: APRI, aspartate aminotransferase/platelet ratio.
Factors Associated with Progressive Course of Disease in US: Large Real-World Database

- PBC patients with elevated ALP levels (>1.5xULN) tend to have a more progressive course
- Aim: To use a large EMR/claims database from the US to assess factors independently associated with this progressive PBC profile
- Methods
  - A database that contained comprehensive and continuous EMR/claims data from >500 healthcare practices or systems from the US (represents about 50% of the entire US population) was utilized
  - PBC patients with or without treatment were divided into ALP < 1.5 x ULN and ALP ≥ 1.5 x ULN (115 U/L was used as ULN)
- Patient population (N=15,875)
  - Age: 63.0 ± 13.5 years
  - Female: 78%
  - Privately insured: 76%
  - Medicaid: 5%
  - Other autoimmune diseases: 57%
  - Cirrhosis: 46%
  - ALP ≥ 1.5xULN: 38.3%

Patients with ALP $\geq 1.5$ULN had longer duration of disease, more cirrhosis, pruritus and jaundice ($p<0.05$)

- In multivariate analysis, older age, female gender, living in Midwest, presence of other autoimmune diseases and compensated cirrhosis were independently associated with having elevated ALP in PBC.

Disease Management
Symptoms Directly Associated with PBC

- Pruritis
- Fatigue
Pruritus Is Common Among PBC Patients

- Prevalence reported as high as 69%\(^1\)
- Unknown etiology\(^1,2\)
  - Bile salts, endogenous opioids, histamine, serotonin, progesterone/estrogen, and autotaxin/lysophosphatidic acid are suspected pruritogens\(^2\)
- Diurnal variation – most intense itch in the late evening\(^2\)
- Localization reported at limbs – soles of feet, palms of hands\(^2\)
- Exacerbated by pregnancy or contact with wool/heat\(^3\)

Schema for the Management of Pruritus

1. Cholestyramine up to 4g × 4 day
2. Rifampicin 150 mg/day
   - Increase up to 60 mg/day every other week
3. Naltrexone up to 50 mg/day
4. Sertraline up to 100 mg/day
5. Extracorporeal albumin dialysis
   - Plasmapheresis
6. Consider transplantation

- Morning and afternoon dose
- Separate 4 hours from other drugs
- Colesevelam if other not tolerated
- Drug induced hepatitis in up to 12%
- Monitor especially first 2 months
- Monitor for (infrequent) hepatotoxicity
- Has not lived up to early hopes

CBD, common bile duct
Assessing and Managing Fatigue

- Though fatigue caused by PBC may not be reversible, associated causes of fatigue should be actively excluded—or identified and managed\(^1,2\)

<table>
<thead>
<tr>
<th>Rule Out:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Associated causes of fatigue (disease or medication):</strong></td>
</tr>
<tr>
<td>• Anemia(^2)</td>
</tr>
<tr>
<td>• Depression(^2)</td>
</tr>
<tr>
<td>• Sleep disorder(^2)</td>
</tr>
<tr>
<td>• Hypothyroidism(^1) (^-) (^3)</td>
</tr>
<tr>
<td>• Medications that can cause or contribute to fatigue (eg, excessive antihypertensive medication)(^1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consider Fatigue Management Strategies:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatigue may be improved by:</strong></td>
</tr>
<tr>
<td>• Maintaining regular physical activity(^4) (^,) (^5)</td>
</tr>
<tr>
<td>• Modafinil (100-200 mg) may be very selectively considered for some patients with severe fatigue in PBC(^*) (^,) (^6)</td>
</tr>
</tbody>
</table>

*Data are limited in PBC, side effects common
# Additional Extrahepatic Complications of PBC

| Metabolic bone disease | • Increased incidence of osteoporosis, osteopenia and risk of fractures  
  • Assess BMD at baseline and every 2 years in PBC patients depending on disease severity |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Hyperlipidemia         | • 75% of patients have total cholesterol levels >200 mg/dL  
  • Atorvastatin and simvastatin are safe and effective for use in PBC |
| Sicca syndrome        | • Associated with dry eyes, dry mouth, vaginal dryness/dyspareunia, an increased frequency of oral candidiasis, and extra-glandular symptoms (i.e., fatigue, arthralgias, myalgias, cytopenias, peripheral neuropathy, vasculitis, Raynaud’s phenomenon)  
  • Treat symptoms according to primary care guidelines |
| Additional manifestations | • Impaired absorption of fat-soluble vitamins A, D, E, and K  
  • Scleroderma  
  • Mixed connective tissue disease  
  • CREST syndrome. |

Hepatic Complications of PBC

- Management of liver-related complications in PBC is the same as the management for patients with advanced liver disease related to other types of chronic liver diseases.

- Management plan should be carried out according to AASLD and ACG guidelines (e.g. screen for HCC, esophageal varices)

Treatment of PBC
Algorithm for Treatment of PBC

US, ultrasound; MRCP, magnetic resonance cholangiopancreatography; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; AMA, anti-mitochondrial antibodies; ANA, antinuclear antibodies; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; OCA, obeticholic acid; HCC, hepatocellular carcinoma; LT, liver transplantation
Ursodeoxycholic Acid/Ursodiol (UDCA)

- Orally administered, naturally occurring, hydrophilic secondary bile acid
- Dose: 13-15 mg/kg/day
- Improvement in liver tests may be seen within a few weeks and 90% of the improvement usually occurs within 6-9 months
- How do you define ”biochemical response” to UDCA?

Abbreviation: UDSA, ursodeoxycholic acid
• After 1 year of treatment, the number of patients with biochemical response according to Paris Criteria was 66% and according to Barcelona Criteria was 62%\(^1\)

• Up to 40% treated with UDCA have a suboptimal response and experience a progressive course\(^2\)

Lack of agreement on the exact definition of non-response; common themes support biochemical response (decrease in ALP) as the most important surrogate for defining response to treatment.

<table>
<thead>
<tr>
<th>Scoring Systems Predicting Non-Response to UDCA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UK-PBC</strong></td>
</tr>
<tr>
<td>Bilirubin, ALP, and AST or ALT at 12 months; Albumin and platelet count at baseline</td>
</tr>
<tr>
<td><strong>GLOBE</strong></td>
</tr>
<tr>
<td>Bilirubin, ALP, albumin, and platelet count at 12 months; Age at baseline</td>
</tr>
<tr>
<td><strong>Non-response after 6 months of treatment with UDCA</strong></td>
</tr>
<tr>
<td>Rochester</td>
</tr>
<tr>
<td>ALP≥2 × ULN or Mayo score ≥ 4.5</td>
</tr>
<tr>
<td>Ehim</td>
</tr>
<tr>
<td>Decrease in GGT ≤ 70% and GGT ≥ 1 × ULN</td>
</tr>
<tr>
<td><strong>Non-response after 12-24 months of treatment with UDCA</strong></td>
</tr>
<tr>
<td>Barcelona</td>
</tr>
<tr>
<td>Lack of decrease in ALP ≤ 40% and ALP ≥ 1.0 × ULN</td>
</tr>
<tr>
<td>Paris-I</td>
</tr>
<tr>
<td>ALP ≥ 3 × ULN or AST ≥ 2 × ULN or bilirubin &gt;1.0</td>
</tr>
<tr>
<td>Rotterdam</td>
</tr>
<tr>
<td>Bilirubin ≥ 1 × ULN and/or albumin &lt; 1 × ULN</td>
</tr>
<tr>
<td>Toronto</td>
</tr>
<tr>
<td>ALP &gt;1.67 × ULN after 2 years on UDCA</td>
</tr>
<tr>
<td>Paris-II</td>
</tr>
<tr>
<td>All three of the following: ALP &gt; 1.5 × ULN, AST &gt; 1.5 × ULN, bilirubin &gt; 1 mg/dl after 1 year on UDCA</td>
</tr>
</tbody>
</table>

Histologic Progression in Untreated Patients and in Patients with Complete vs Incomplete UDCA Biochemical Response

Angulo et al. *Hepatol*, 1999

Kumagi et al. *Am. J. Gastroenterol*, 2010

% of Patients with Worsening Stage

**5-9 Years of Treatment**

- Untreated (n=51)
- UDCA (n=16)

**10 Years of Treatment**

- UDCA Response (n=39)
- UDCA Non-response (n=30)

UDCA: Transplant-free Survival Based on Bilirubin and Alkaline Phosphatase Levels at 1 Year Follow-up

Criteria for Adding
Second-Line Treatment (OCA)

- Persistently elevated serum ALP after 12 months of therapy with UDCA
- Lack of normalization of bilirubin after 12 months of therapy with UDCA
- High risk using available predictive models (UK-PBC, GLOBE PBC)
- Evidence of fibrosis progression by any modality (TE, MRE, histology or clinically) while on UDCA
- Progression to cirrhosis by any definition

ALP, alkaline phosphatase; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; OCA, obeticholic acid; TE, transient elastography; MRE, magnetic resonance elastography
FXR Agonist

Bile Acid Homeostasis
- Decreases BA synthesis
- Decreases BA uptake
- Decreases BA absorption
- Increases BA secretion

Inflammation Pathways
- Down-regulates NF-KB, TNF
- Decreases IgM and CRP

CHOLERESIS

Abbreviations: BA, bile acid; NF-KB, nuclear factor kappa beta; TNF, tumor necrosis factor; CRP, C-reactive protein
POISE: Double-Blind and Open-Label Extension Design

If on UDCA: Continue UDCA

| Screening | Placebo ± UDCA (n=73) | OCA 5-10 mg ± UDCA (n=70)† | OCA 10 mg ± UDCA (n=73) |

All patients initiated OCA 5 mg for 3 months, after which patients had the option to titrate based on tolerability

Visits every 3 months

0 DB W2 DB M3 DB M6 DB M9 DB M12/ OLE 0 OLE M36

- Key inclusion criteria: PBC diagnosis, alkaline phosphatase (ALP) ≥1.67x upper limit of normal (ULN) and/or total bilirubin >ULN to <2x ULN, stable UDCA dose or unable to tolerate UDCA
- Primary endpoints: Achieving ALP <1.67x ULN with a ≥15% reduction in ALP and total bilirubin ≤ULN, and long-term safety and tolerability
- Secondary endpoints: Effect of OCA on markers of cholestasis and hepatic function and damage

Primary Endpoint in the Double-Blind and Open-Label Extension Phases

No. of Patients

<table>
<thead>
<tr>
<th>Month in Double-Blind Phase</th>
<th>Placebo</th>
<th>Obeticholic acid, 5-10 mg</th>
<th>Obeticholic acid, 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>73</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>73</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>73</td>
<td>73</td>
<td>73</td>
</tr>
<tr>
<td>12</td>
<td>73</td>
<td>70</td>
<td>70</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Month in Open-Label Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>12</td>
</tr>
</tbody>
</table>

Alkaline Phosphatase in the Double-Blind and Open-Label Phases

A Alkaline Phosphatase

No. of Patients
Placebo 73 69 71 69 70 64 60 59 59
Obeticholic acid, 5-10 mg 70 69 69 66 64 63 62 62 60
Obeticholic acid, 10 mg 73 66 64 64 62 64 59 61 59

Sustained Improvements in ALP Through 48 Months of OCA Treatment

<table>
<thead>
<tr>
<th>Mean (SD) Change from OCA Baseline ALP (U/L)</th>
<th>Total OCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>△ 12 Months†</td>
<td>-105.2 (87.6)***</td>
</tr>
<tr>
<td>△ 24 Months†</td>
<td>-101.0 (98.5)***</td>
</tr>
<tr>
<td>△ 36 Months†</td>
<td>-108.6 (95.7)***</td>
</tr>
<tr>
<td>△ 48 Months†</td>
<td>-95.6 (121.1)***</td>
</tr>
</tbody>
</table>

***p<0.0001; †DB Placebo patients: OCA Baseline is the last assessment prior to the first OCA dose in the OLE; DB OCA patients: OCA Baseline is the mean of all available evaluations prior to DB treatment. ‡p-value for the within treatment comparisons are obtained using a paired t-test. Trauner M, et al. Presented at EASL, 53rd International Congress; 2018; Paris, France (Poster 216).
Total Bilirubin During the Double-Blind and Open-Label Phases

Total Bilirubin Remained Stable Through 48 Months of OCA Treatment

![Graph showing total bilirubin levels over time](image)

<table>
<thead>
<tr>
<th>Mean (SD) Change from OCA Baseline Total Bilirubin (µmol/L)</th>
<th>Total OCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆ 12 Months‡</td>
<td>-0.9 (4.1)**</td>
</tr>
<tr>
<td>∆ 24 Months‡</td>
<td>-0.1 (5.3)</td>
</tr>
<tr>
<td>∆ 36 Months‡</td>
<td>-0.6 (4.1)</td>
</tr>
<tr>
<td>∆ 48 Months‡</td>
<td>-0.8 (3.8)*</td>
</tr>
</tbody>
</table>

Patients receiving Placebo during the 12-month DB phase received OCA for 36 months during the OLE. Patients receiving OCA during the 12-month DB phase received OCA for 36 months during the OLE (total of 48-month OCA treatment).

*p<0.05, **p<0.01; †DB Placebo patients: OCA Baseline is the last assessment prior to the first OCA dose in the OLE; DB OCA patients: OCA Baseline is the mean of all available evaluations prior to DB treatment. ‡p-value for the within treatment comparisons are obtained using a paired t-test.

Other Findings on Obeticholic Acid in POISE

- Obeticholic acid is associated with statistically significant, clinically meaningful improvements\(^1\)
  - Biochemical criteria correlated with clinical benefit (alkaline phosphatase and bilirubin)
  - Markers of inflammation (C-reactive protein) and apoptosis (CK18)
- Efficacy and safety of obeticholic acid
  - Demonstrated when analyzed according to disease severity/response criteria\(^2\)
  - Consistent across patient subgroups\(^3\)
    - Age at diagnosis
    - Disease duration
    - Baseline alkaline phosphatase levels

Patients receiving Placebo during the 12-month DB phase received OCA for 36 months during the OLE. Patients receiving OCA during the 12-month DB phase received OCA for 36 months during the OLE (total of 48-month OCA treatment).

†AEs ≥15%; Percentages are based on the total number of patients during the OLE.

‡Safety Population (data cutoff 01 Aug 2017).


### Adverse Events†:
Double-Blind Phase and Open Label-Extension

<table>
<thead>
<tr>
<th>Preferred Term, n (%)</th>
<th>DB Placebo</th>
<th>DB OCA 5-10 mg</th>
<th>DB OCA 10 mg</th>
<th>Total OCA‡ n=193</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Adverse Events (AEs)</td>
<td>66 (90)</td>
<td>65 (93)</td>
<td>69 (95)</td>
<td>190 (98)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>28 (38)</td>
<td>39 (56)</td>
<td>50 (68)</td>
<td>149 (77)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (14)</td>
<td>11 (16)</td>
<td>17 (23)</td>
<td>63 (33)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>13 (18)</td>
<td>17 (24)</td>
<td>13 (18)</td>
<td>51 (26)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8 (11)</td>
<td>4 (6)</td>
<td>4 (5)</td>
<td>45 (23)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (4)</td>
<td>4 (6)</td>
<td>7 (10)</td>
<td>43 (22)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (12)</td>
<td>4 (6)</td>
<td>8 (11)</td>
<td>36 (19)</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (7)</td>
<td>4 (6)</td>
<td>6 (8)</td>
<td>33 (17)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>8 (11)</td>
<td>4 (6)</td>
<td>4 (5)</td>
<td>32 (17)</td>
</tr>
<tr>
<td>Back pain</td>
<td>8 (11)</td>
<td>4 (6)</td>
<td>4 (5)</td>
<td>28 (15)</td>
</tr>
</tbody>
</table>
Days of Pruritus per Patient Year in Patients Treated with Placebo and OCA$^\S$

$^\S$Patients receiving Placebo during the 12-month DB phase period received OCA for 36 months during the OLE. Patients receiving OCA during the 12-month DB period received OCA for 36 months during the OLE (total of 48-month OCA treatment).

$^\S$Event days per patient year on study is the sum of each patient's days of pruritus event divided by the total patient years on study.

POISE Substudy of Fibrosis Progression

- Evaluated the effect of 3 years of OCA therapy in patients with an inadequate response to UDCA on fibrosis progression using paired liver biopsies
- Patients enrolled into POISE had the option to participate in a biopsy substudy
  - Patients were required to have a baseline biopsy ≤1 year from Day 0 of the double-blind (DB) period
  - Follow-up biopsy was to occur after 3 years of treatment with OCA
    - DB + 2 years of open-label extension (OLE) if randomized to OCA
    - DB + 3 years of OLE on OCA if randomized to placebo during DB phase
- Biopsies were centrally read
Demographics and PBC Disease Characteristics

Biopsy Cohort (N=13)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Biopsy Cohort (N=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>58 (46, 76)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>12 (92)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>11 (85)</td>
</tr>
<tr>
<td>Europe, n (%)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>North America, n (%)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Duration of PBC, years</td>
<td>9.4 (1.7, 21.3)</td>
</tr>
<tr>
<td>History of PBC-related pruritus, n (%)</td>
<td>11 (85)</td>
</tr>
<tr>
<td>UDCA usage, n (dose, mg/kg)</td>
<td>13 (13.5)</td>
</tr>
<tr>
<td>ALP, U/L</td>
<td>322 (213, 530)</td>
</tr>
<tr>
<td>Total bilirubin, µmol/L</td>
<td>6.2 (3.9, 15.1)</td>
</tr>
<tr>
<td>Direct bilirubin, µmol/L</td>
<td>1.5 (1.5, 10.5)</td>
</tr>
<tr>
<td>Fibrosis stage (F1/F2/F3/F4/F5)</td>
<td>1/3/5/2/2</td>
</tr>
<tr>
<td>Biopsy Timing (years, range)</td>
<td></td>
</tr>
<tr>
<td>First dose of OCA to follow-up biopsy</td>
<td>3.0 (2.9-3.0)</td>
</tr>
<tr>
<td>Baseline biopsy to follow-up biopsy</td>
<td>3.8 (2.9-4.1)</td>
</tr>
</tbody>
</table>

Patients with a biopsy at baseline
N=27

- Patients with paired biopsies
N=15

- Baseline Biopsy Only, N=12
  - 4 Continued in POISE
  - 2 Discontinued due to pruritus
  - 1 Discontinued due to other AEs
  - 2 Discontinued due to other reasons
  - 3 Withdrew consent

- 2 Patients excluded due to inadequate sample
  - 1 Patient had a 1-mm biopsy length
  - 1 Patient had a 5-mm biopsy length in 2 fragments

- 2 Patients with a biopsy at baseline
N=27

- Patients with paired biopsies
N=15

- Patients with paired biopsies sufficient for analysis
N=13

Data are median (min, max) unless otherwise indicated.
The Majority of Patients Had Reversal or Stabilization in Fibrosis Stage After 3 Years of OCA Treatment

- Six patients (46%) showed reversal in fibrosis (1 stage, n=4; 2 stages, n=2), while 2 patients (15%) showed fibrosis worsening by 1 stage.
- All 4 patients with baseline cirrhosis showed reversal of fibrosis by at least 1 stage, and 3 (75%) improved to fibrosis without cirrhosis.

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

## Recommended Dosing (US Label)

<table>
<thead>
<tr>
<th>Staging/Classification</th>
<th>Non-Cirrhotic or Compensated Child-Pugh Class A</th>
<th>Child-Pugh Class B or C or Patients with a Prior Decompensation Event&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting OCALIVA Dosage for first 3 months</strong></td>
<td>5 mg once daily</td>
<td>5 mg once weekly</td>
</tr>
<tr>
<td><strong>OCALIVA Dosage Titration after first 3 months, for patients who have not achieved an adequate reduction in ALP and/or total bilirubin and who are tolerating OCALIVA&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>10 mg once daily</td>
<td>5 mg twice weekly (at least 3 days apart)</td>
</tr>
<tr>
<td><strong>Maximum OCALIVA Dosage</strong></td>
<td>10 mg once daily</td>
<td>10 mg twice weekly (at least 3 days apart)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Gastroesophageal variceal bleeding, new or worsening jaundice, spontaneous bacterial peritonitis, etc.

<sup>b</sup> Prior to dosage adjustment, re-calculate the Child-Pugh classification.
Summary

- PBC is most commonly diagnosed in middle-aged women
- Taking a good history is essential
- Diagnosis can typically be made based on persistent cholestatic liver profile and AMA positivity after other common liver diseases have been excluded
- Manage patient with UDCA and/or OCA based on response
Long-Term Management of Patients with PBC

- Liver tests every 3-6 months \(\Rightarrow\) **consider OCA if non response to UDCA**
- Thyroid status (TSH) annually
- DEXA at baseline and every 2-4 years
- Monitor for associated autoimmune conditions
- In the presence of severe cholestasis \(\Rightarrow\) assess levels of vitamins A and D. May need to administer Vit K prior to procedures
- Upper endoscopy every 1-3 years if cirrhotic or Mayo risk score >4.1
- Ultrasound ± AFP every 6 months in patients with known or suspected cirrhosis

Case #1
Case #1: Newly Diagnosed

- 56-year-old white female presents to primary care provider for routine annual exam
- Reports fatigue and intermittent itching
- Only medication is levothyroxine; no OTC products
- BMI = 29; no metabolic syndrome
- ALP 310 U/L, AST 55 U/L, ALT 81 U/L, total bilirubin 0.7 g/dL, hemoglobin 12.5 mg/dL, platelets 195K
- Viral hepatitis serologies negative
Case #1: Newly Diagnosed

- GP recommends abdominal ultrasound which shows normal liver/spleen morphology, no bile duct dilatation and normal gall bladder.
- Patient referred to you.
- What additional tests would you order?
Case #1: Newly Diagnosed

• Results
  – AMA 1:320, ANA 1:160, ASMA neg, IgG 1560, IgM 350

• Would you need a liver biopsy
  – To diagnose PBC for this patient?
  – To stage disease for this patient?

• Could you use transient elastography (e.g., Fibroscan) to get the diagnosis/staging?

• Going forward, don’t lose sight of ongoing patient management: DEXA, mammogram, vitamin levels
Case #2
52 year old female

Diagnosed in 2009 when an elevated alkaline phosphatase (ALP) (335 U/L) was worked up

Prescribed UDCA (14 mg/kg) in 2009 and has been taking it ever since

Was unemployed from 2012-2014 and was poorly adherent

Back on UDCA 14 mg/kg and adherent since 2014

Fatigue, pruritus, and Sicca syndrome

Cholestyramine as needed
Case #2: Currently Managed with UDCA

- Platelets have dropped from 200K to 130K since diagnosis
- DEXA, mammogram, vitamins, thyroid tests
- ALP has remained between 175-260 U/L between 2010-now
- Splenomegaly
Case #2: What Would You Do Next?

- Would you do a liver biopsy?
- EGD?
- Would you increase the dose of UDCA?
- Would you add obeticholic acid to UDCA?
  - Which dose?

Abbreviations: EGD, esophagogastroduodenoscopy
For more information or for additional CME offerings, please visit www.chronicliverdisease.org

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