THE CHRONIC LIVER DISEASE FOUNDATION PRESENTS

EXPERT PERSPECTIVES ON THE MANAGEMENT OF PBC

A CASE-BASED APPROACH

This symposium is not affiliated with UEG. Supported by an educational grant from Intercept Pharmaceuticals, Inc.
Welcome and Introduction

Gideon Hirschfield
Vienna October 2016
University of Birmingham
Cynthia Levy, MD
Associate Professor of Medicine
Program Director, Transplant Hepatology Fellowship
Division of Hepatology
University of Miami Medical School
Miami, Florida, USA

Gideon M. Hirschfield, MA MB BChir FRCP PhD
Professor/Honorary Consultant Hepatologist
Centre for Liver Research
University of Birmingham
Birmingham, United Kingdom
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- **Grants/Research Support:** Falk Pharma (unrestricted)
- **Consultant/Speaker Bureau:** Falk Foundation, Intercept
- **Advisory Board Membership:** Intercept, GSK, Novartis

Cynthia Levy
- **Grants/Research Support:** Intercept, Gilead, NGM, Cyma Bay, Tobira, Novartis, GSK, Shire, Shionogi
- **Consultant/Speaker Bureau:** Novartis, Intercept, Target Pharmasolutions
- **Advisory Board Membership:** Intercept
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Lisa D. Pedicone, PhD, Medical Writer, Chronic Liver Disease Foundation - No Relevant Relationships

All other Chronic Liver Disease Foundation and Annenberg Center staff have no relevant relationships to disclose.
The Chronic Liver Disease Foundation would like to thank

**Intercept Pharmaceuticals, Inc.**

for providing an educational grant to support this educational program.
Educational Objectives

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

• Discuss epidemiology, diagnosis and staging of PBC
• Recognize the limitations of current therapies and understand how emerging therapies can improve patient outcomes
• Develop evidence-based treatment strategies using the latest clinical data
The Vision of the Future

• Better treatment targeted in better ways encompassing quantity and quality of life

• Key attributes of safe, tolerable and effective therapy:
  – Targeted for patients with unmet need through appropriate risk stratification
  – Proof of benefit in studies of appropriate patient cohorts
  – Manageable and tolerable side effects
Diagnosis, Risk Stratification and Current Management

Cynthia Levy, MD, AGAF, FAASLD
University of Miami
Miller School of Medicine
Miami, Florida, USA
Diagnosis

• 2 out of 3 criteria:
  – Chronic unexplained elevation of ALP
  – Presence of anti-mitochondrial antibodies $\geq 1:40$
  – Histology:
    • Lymphoplasmacytic infiltrates in the portal area
    • Non suppurative destructive cholangitis
    • Granulomas
    • Bile duct loss

• Symptoms:
  – Pruritus, fatigue, sicca symptoms

AASLD and EASL guidelines
Destructive Cholangitis

Courtesy of Dr Monica Garcia Buitraga
Risk Stratification

• Clinical Presentation
  – Age/gender – younger patients and males do worse
  – Variant syndromes

• Risk of critical outcome
  – Disease stage
  – Serological profile
  – Response to UDCA
Staging

- Transient elastography
- MR elastography
- APRI (AST/platelet ratio)
- ELF (enhanced liver fibrosis score)
- Liver biopsy
  - Diagnosis of AMA negative PBC
  - R/o overlap with AIH and premature ductopenic variants
  - Evaluation of non responders to UDCA
Liver Stiffness

- **LS > 9.6 at baseline** associated with 5x increase in risk of adverse outcomes
- **LS increase >2.1 kPa/year** associated with 8x increase in risk of adverse outcomes

**Serology**

- **Gp210 ➔ Present in 10%; associated with more interface hepatitis, more aggressive disease, hepatic failure phenotype**
- **Sp100 ➔ present in 20-30%, highly specific, no association with prognosis**
- **Centromere ➔ associated with portal hypertension phenotype in PBC**

![Anti gp 210 in HEP2 cells.](source: Expert Rev Mol Diagn © 2011 Expert Reviews Ltd)
Models for Risk Stratification

Dichotomous

- Barcelona, Paris, Toronto, Mayo, Rotterdam
- Easy to use
- Imply only 2 levels of risk

Continuous

- UK PBC, Globe PBC score
- Outperform dichotomous models
- Take into consideration continuous relationship between variable and risk of death/LT
Combined Effect of Total Bilirubin and Alkaline Phosphatase on Transplant-Free Survival

Globe Score for PBC:
www.globalPBC.com/globe/

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

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

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<th>Upper limit of normal:</th>
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<td><strong>Age, years</strong> at initiation of UDCA therapy</td>
<td></td>
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<tr>
<td><strong>Total bilirubin level, µmol/L or mg/dl</strong> after one year of UDCA therapy</td>
<td></td>
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<tr>
<td><strong>Alkaline phosphatase level, U/L</strong> after one year of UDCA therapy</td>
<td></td>
</tr>
<tr>
<td><strong>Albumin, g/L</strong> after one year of UDCA therapy</td>
<td></td>
</tr>
<tr>
<td><strong>Platelets, x 10^9/L</strong> after one year of UDCA therapy</td>
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# Globe Score for PBC

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

<table>
<thead>
<tr>
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<th>GLOBE score:</th>
<th>Liver transplant-free survival</th>
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<tbody>
<tr>
<td></td>
<td>0.46</td>
<td></td>
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<tr>
<td><strong>GLOBE score</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Liver transplant-free</strong></td>
<td></td>
<td></td>
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<tr>
<td>survival</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>3-year</td>
<td>94.6%</td>
</tr>
<tr>
<td></td>
<td>5-year</td>
<td>90.5%</td>
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<tr>
<td></td>
<td>10-year</td>
<td>76.4%</td>
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## Table

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<th>Value</th>
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<td>Age, years at initiation of UDCA therapy</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin level, µmol/L or mg/dl after one year of UDCA therapy</td>
<td>1</td>
<td>Upper limit of normal: 1</td>
</tr>
<tr>
<td>Alkaline phosphatase level, U/L after one year of UDCA therapy</td>
<td>260</td>
<td>Upper limit of normal: 130</td>
</tr>
<tr>
<td>Albumin, g/L after one year of UDCA therapy</td>
<td>4</td>
<td>Lower limit of normal: 4</td>
</tr>
<tr>
<td>Platelets, x 10^9/L after one year of UDCA therapy</td>
<td>150</td>
<td></td>
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New Diagnosis

- Baseline Evaluation
  - Imaging & Labs
  - Assess symptoms
  - Staging
  - DEXA
- Initiate PBC-specific therapy
  - UDCA 13-15 mg/kg/day
- Long-term monitoring
  - Clinical evaluation
  - Biochemistries
  - Transient elastography

Pruritus
Fatigue
Sicca Syndrome

Cirrhosis? MRS > 4.5? Thrombocytopenia
Risk stratification after 1 year of therapy
Evaluate need for adjuvant therapy

EGD; HCC surveillance
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; IgM, immunoglobulin M; TB, total bilirubin; UDCA, ursodeoxycholic acid.
Graphic courtesy of Dr. Cynthia Levy.
• Non responders to UDCA
  – Increased risk of hepatic decompensation, death or liver transplantation
  – Increased risk of hepatocellular carcinoma
Summary

• PBC is a heterogeneous disease
• Patient care must be individualized
• Once diagnosis is made efforts should be geared towards staging
  – Labs, elastography
• Long term monitoring
  – Risk stratification: Evaluate response 1 year after UDCA is started
  – Determine need for adjuvant therapy
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Management of PBC: New and Future Treatments

Gideon Hirschfield

Vienna October 2016
University of Birmingham, UK
PBC Care Pathway

**CHOLESTATIC LIVER BIOCHEMISTRY WITHOUT IMMEDIATE EXPLANATION**

**LIVER SCREEN**
- inc. USS abdomen, autoantibodies (AMA, ANA), immunoglobulins, liver biopsy if indicated
- AMA (>1 in 40) or PBC specific ANA or consistent liver histology

**Negative liver screen**

**FURTHER INVESTIGATION AS CLINICALLY APPROPRIATE**

**CLINICAL DIAGNOSIS OF PBC**

**TREAT & RISK STRATIFY**
- UDCA for all (13-15mg/kg/day)
- ASSESS BIOCHEMICAL RESPONSE AT 1 YEAR
  - UDCA Responder (Low Risk Disease)
  - Inadequate UDCA Responder e.g. ALP >1.67xULN
  - TAILORED FOLLOW-UP according to symptom burden and disease stage
  - REFER TO EXPERT CENTRE
    - Second line therapy?
    - Clinical trials?
    - Liver biopsy?

**STAGE & SURVEY**
- DISEASE STAGING E.G. ULTRASOUND, ELASTOGRAPHY, ELF SCORE
- CIRRHOSIS
  - Rising bilirubin and/or decompensated disease
  - REFER TO EXPERT CENTRE / TRANSPLANT CENTRE
- HCC + VARICES SCREENING

**ACTIVELY MANAGE**
- SYMPTOM EVALUATION/ACTIVE MANAGEMENT
  - Pruritus
  - Fatigue
  - Bone density
  - Co-existent autoimmune disease
- PATIENT MANAGEMENT AS PER GUIDELINES
  - Intractable symptoms
  - REFER TO EXPERT CENTRE
    - Clinical trials?
New Therapeutic Opportunities

**Bile Acids**
- FXR/FGF19 axis?
- Microbiome manipulation?
- PPARs?
- Bile acid uptake inhibition?
- Augment HCO$_3^-$ secretion?

**Immunoregulation**
- Secretome inhibitors?
- Immunomodulation?
- Cell recruitment & adhesion?

**BEC Injury and its response**
- Down-regulation of AE2 sensitizes cholangiocytes to apoptotic insults

**Fibrosis**
- Epithelial protectants?
- Anti-fibrotics?
Ustekinumab and PBC

## Pharmacologic agents under study (examples)

<table>
<thead>
<tr>
<th>Targets</th>
<th>Natural ligands (examples)</th>
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<tbody>
<tr>
<td><strong>Nuclear receptors</strong></td>
<td></td>
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<tr>
<td>Obeticholic acid, PX-102, GS-9674, LJN452, EDP-305, AKN-083</td>
<td>FXR</td>
</tr>
<tr>
<td>All-trans retinoic acid</td>
<td>RXR</td>
</tr>
<tr>
<td>Bezafibrate, fenofibrate, ciprofibrate</td>
<td>PPARa</td>
</tr>
<tr>
<td>MBX-8025</td>
<td>PPAR delta agonist</td>
</tr>
<tr>
<td>Budesonide and other corticosteroids</td>
<td>GR, PXR</td>
</tr>
<tr>
<td>Rifampicin, statins, corticosteroids</td>
<td>PXR</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>VDR</td>
</tr>
<tr>
<td><strong>Membrane receptors</strong></td>
<td></td>
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<tr>
<td>FGF19, NGM 282</td>
<td>FGFR4</td>
</tr>
<tr>
<td>Int-777</td>
<td>TGR5</td>
</tr>
<tr>
<td>ASBT inhibitors</td>
<td>ASBT</td>
</tr>
<tr>
<td><strong>Bile acid derivatives</strong></td>
<td></td>
</tr>
<tr>
<td><em>norUDCA</em></td>
<td>?</td>
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</table>
Biochemical endpoint as primary measure of efficacy: ALP <1.67 x ULN with normal bilirubin and ≥15% ALP reduction

Risk stratified population: ALP ≥1.67 x ULN and/or bilirubin >ULN but <2 x ULN

Obeticholic acid: Phase III Randomised Controlled Trial

CONSORT Diagram (Double-Blind Phase)

316 Participants were assessed for eligibility
- 99 Screen failures: 63 (64%) biochemistry, 13 (13%) medications, 5 (2%) pruritus

217 Participants were randomized
- 1 Withdraw prior to dosing

215 Participants received drug for the intent-to-treat population

73 Assigned to receive placebo
70 Assigned to receive obeticholic acid, 5 - 10 mg
73 Assigned to receive obeticholic acid, 10 mg

69 Completed Month 6 visit
- 32 Ineligible for titration remained at obeticholic acid, 5 mg
- 37 Eligible for titration to obeticholic acid, 10 mg

4 Continued at obeticholic acid, 5 mg
33 Titrated from obeticholic acid, 5 mg to 10 mg

7 Discontinued
- 2 Withdraw consent
- 1 Withdraw due to pruritus
- 3 Had other adverse events
- 1 Death

5 Discontinued
- 1 Withdraw consent
- 1 Withdraw due to pruritus
- 1 Had other adverse event

70 Completed Month 12 visit
64 Completed Month 12 visit
64 Completed Month 12 visit

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Primary Composite End Point in the Double-Blind and Open-Label Extension Phases, According to Trial Group

- **Placebo**
- **Obeticholic acid, 5-10 mg**
- **Obeticholic acid, 10 mg**

**Double-Blind Phase**

**Open-Label Phase**

- 5 mg
- Dose adjustment

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Rapid and Durable Effect

A Alkaline Phosphatase

Double-Blind Phase

Open-Label Phase

Month in Double-Blind Phase

Month in Open-Label Phase

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Placebo</th>
<th>Obeticholic acid, 5-10 mg</th>
<th>Obeticholic acid, 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>73</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>69</td>
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<td>66</td>
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<td>59</td>
<td>59</td>
<td>59</td>
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Effect is Greater than Just the Dichotomous Primary End Point

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Biologic Correlates

OCA is currently not licensed in the EU
## Table 2. Incidence of Adverse Events of 10% or More in any Treatment Group.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=73)</th>
<th>OCA, 5-10 mg (N=70)</th>
<th>OCA, 10 mg (N=73)</th>
<th>Total OCA (N=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>28 (38)</td>
<td>39 (56)</td>
<td>50 (68)</td>
<td>138 (72)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>13 (18)</td>
<td>17 (24)</td>
<td>13 (18)</td>
<td>45 (23)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (18)</td>
<td>12 (17)</td>
<td>6 (8)</td>
<td>36 (19)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (14)</td>
<td>11 (16)</td>
<td>17 (23)</td>
<td>50 (26)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (12)</td>
<td>4 (6)</td>
<td>8 (11)</td>
<td>28 (15)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (11)</td>
<td>2 (3)</td>
<td>8 (11)</td>
<td>17 (9)</td>
</tr>
<tr>
<td>Back pain</td>
<td>8 (11)</td>
<td>4 (6)</td>
<td>4 (5)</td>
<td>24 (12)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>8 (11)</td>
<td>4 (6)</td>
<td>4 (5)</td>
<td>20 (10)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8 (11)</td>
<td>4 (6)</td>
<td>4 (5)</td>
<td>31 (16)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>8 (11)</td>
<td>4 (6)</td>
<td>0</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (4)</td>
<td>4 (6)</td>
<td>7 (10)</td>
<td>32 (17)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>3 (4)</td>
<td>11 (16)</td>
<td>8 (11)</td>
<td>27 (14)</td>
</tr>
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OCA Monotherapy: Alkaline Phosphatase Reductions Through Year 5

Graphic courtesy of Intercept Pharmaceuticals.
Double-blind, Placebo-controlled trial of NGM282 Patients with PBC and Incomplete Response to UDCA (n = 45; 28 days)

ClinTrials NCT02026401
A randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of repeat doses of GSK2330672 administration in patients with PBC and symptoms of pruritus

• Statistically significantly decrease in pruritus severity with the selective ASBT inhibitor GSK2330672 compared to placebo:
  
  – **Reduction of pruritus within the first week of GSK2330672**, continued to decrease through 2 weeks of treatment and returned towards baseline upon blinded switch to placebo.
  
  – Decreases in sleep disturbance and overall disability (5D itch scale) also noted upon GSK2330672 administration compared to placebo.
  
  – Statistically significant target engagement by GSK2330672 was demonstrated by
    
    • Considerable decrease in concentration of serum total Bile acids, and increase in serum C-4
    
    • 33% incidence of diarrhoea reported while on GSK2330672 vs. 5% on placebo.

Conclusions

- The era of stratified care for patients with PBC is present
- Identifying patients at risk of disease progression on standard-of-care UDCA is readily achievable with laboratory-based stratification tools
- New therapies are rapidly approaching the clinic (e.g. Obeticholic acid and others), driving optimism of rational therapy for patient benefit
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Case #1: The High-Risk Patient

Gideon Hirschfield
Vienna October 2016
University of Birmingham
Case 1: Mrs. P

- 40 year old hairdresser

- **Background medical history:**
  - Recurrent urinary tract infections (UTI)
  - Non-smoker, non-drinker

- Presented in 2012 with fatigue
  - ALP 1500, AST 150, Bilirubin 9, albumin 41, platelets 143
  - AMA positive and ANA positive

- **Diagnosis:** PBC
High-risk baseline features for disease progression

- Presenting age: 40 yrs.
- Fatigued
- ANA positive: anti-gp210 +ve and sp100 positive
- APRI: 2.62
- Fibroscore: 15.3 kPa

- May 2012: Started on UDCA
  - 1000 mg / day = 15.3 mg / kg
Mrs. P

- At one year
  - Bilirubin 9
  - Albumin 41
  - AST 88
  - ALT 120
  - ALP 439
  - Platelets: 133
Mrs. P: Response to UDCA

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

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

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<td>9</td>
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<td>Upper limit of normal</td>
<td>22</td>
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<tr>
<td>Alkaline phosphatase level, U/L after one year of UDCA therapy</td>
<td>439</td>
</tr>
<tr>
<td>Upper limit of normal</td>
<td>105</td>
</tr>
<tr>
<td>Albumin, g/L after one year of UDCA therapy</td>
<td>41</td>
</tr>
<tr>
<td>Lower limit of normal</td>
<td>34</td>
</tr>
<tr>
<td>Platelets, x10^9/L after one year of UDCA therapy</td>
<td>133</td>
</tr>
</tbody>
</table>

Interpretation of the GLOBE score:

Patients with a GLOBE score corresponding with a transplant-free survival comparable with a healthy population are at low risk for future adverse events and patients with a GLOBE score corresponding with a transplant-free survival that significantly deviates from a healthy population may benefit from new therapies.

Data of the healthy population, a population with a life-expectancy comparable with that of other countries participating in the Global PBC Study Group, were retrieved from a Dutch registry (Statistics Netherlands, www.cbs.nl).

Mrs. P: Clinical Course

High Risk

- Developed varices
- Intermittent itch
- More itch, Ankle swelling

**ALP (IU/L):**
- 1500 to 374

**Platelet count:**
- 150 to 111

**AST (IU/L):**
- 150 to 111

**Bilirubin μmol/L:**
- 7 to 17

Year:
- 2012 to 2016
PBC Care Pathway

**CLINICAL DIAGNOSIS OF PBC**

**TREAT & RISK STRATIFY**

- **UDCA**
  - for all (13-15mg/kg/day)
  - **ASSESS BIOCHEMICAL RESPONSE** AT 1 YEAR

- **UDCA Responder (Low Risk Disease)**
- **Inadequate UDCA Responder**
  - e.g. ALP >1.67xULN
- **TAILORED FOLLOW-UP**
  - according to symptom burden and disease stage

- **REFER TO EXPERT CENTRE**
  - Second line therapy?
  - Clinical trials?
  - Liver biopsy?

**STAGE & SURVEY**

- **DISEASE STAGING**
  - E.G. ULTRASOUND, ELASTOGRAPHY, ELF SCORE
  - **CIRRHOSIS**
    - Rising bilirubin and/or decompensated disease
    - **REFER TO EXPERT CENTRE / TRANSPLANT CENTRE**
    - **HCC + VARICES SCREENING**

**ACTIVELY MANAGE**

- **SYMPTOM EVALUATION/ACTIVE MANAGEMENT**
  - Pruritus
  - Fatigue
  - Bone density
  - Co-existent autoimmune disease

- **PATIENT MANAGEMENT AS PER GUIDELINES**
  - Intractable symptoms
  - **REFER TO EXPERT CENTRE**
    - Clinical trials?
Case #2 – The Symptomatic Patient

Cynthia Levy, MD
Vienna October 2016
University of Miami
• 56 year old white female presented to general practitioner for routine annual evaluation.
  – Asymptomatic
  – Labs: ALP 440, AST 54, ALT 75, TB 0.7, Hb 12, Plat 205
• GP recommended US abdomen, which showed normal liver/spleen morphology, no bile duct dilatation. Normal GB.
• Only medication was Synthroid. No OTC products. Viral hepatitis serologies were negative. Patient referred to you.
• You ordered additional tests:
  – AMA 1:320, ANA 1:160, ASMA neg, IgG 1560, IgM 350
  – Diagnosis of Primary Biliary Cholangitis is made
  – Plan to initiate UDCA 15 mg/kg/day
  – Transient elastography: 8.6 kPa

• Which symptoms should we ask about?
  – Pruritus – 40-70%
  – Fatigue – 40-80%
  – Dry eyes
  – Dry mouth 30-50%
• You ordered additional tests:
  – AMA 1:320, ANA 1:160, ASMA neg, IgG 1560, IgM 350
  – Diagnosis of PBC is made
  – Plan to initiate UDCA 15 mg/kg/day
  – Transient elastography: 8.6 kPa
• Which symptoms should we ask about?
  – Pruritus ➔ “None”
  – Fatigue ➔ “Mild, but I handle well. I can get my chores done”
  – Dry eyes ➔ “Yes, is it related??”
  – Dry mouth ➔ “funny you asked – my dentist said I have significant dental decay and seem to lack saliva!”
Sicca Syndrome

- Dry eyes
- Dry mouth
- Vaginal dryness/dyspareunia
- Increased frequency of oral erythematous candidiasis
- Extra-glandular symptoms: fatigue, arthralgias, myalgias, cytopenias, peripheral neuropathy, vasculitis, Raynaud’s
- Association with non-Hodgkin’s lymphoma
Follow-up

• At 6 months:
  – Dry eyes and dry mouth under control
  – DEXA scan was normal
  – Labs: ALP 310, AST 33, ALT 39, TB 0.6, Plat 200

• At 12 months:
  – Compliant with medications
  – Labs: ALP 270, AST 35, ALT 40, TB 0.6, Plat 200
  – You decide to start OCA
Changes in ALP Over Time

OCA started
Mild itching
What now?

ALP
ALP Change in the Titration Group

Based on this information - increased OCA to 10 mg/day

Figure S2. ALP Change from Baseline in the Obeticholic Acid, 5-10 mg Group (Double-Blind Phase)
Mean (SD) ALP (U/L) change from baseline values during the double-blind phase for patients that completed the month 6 visit remaining on obeticholic acid, 5 mg compared to patients who uptitrated to 10 mg following the month 6 visit.
***p<0.001; p-values are within treatment comparisons using a paired t-test.
Follow-up

Developed significant itching: VAS 6
Pruritus

- 40-70% of patients with PBC have pruritus at baseline; 15% severe
  - Pruritus is the most common side effect of OCA
  - Dose-dependent
  - Fewer drug discontinuations when starting at 5 mg/day
- No correlation with disease stage
- More common in the extremities; exacerbated by heat and pressure
- Diurnal fluctuation
- When severe: sleep disturbance, inability to carry on daily activities, depression, poor quality of life

Stepwise Approach to Itch

Cholestryamine (4-16 g/day)  
Anion exchange resin  
- Difficult posology  
- Bloating, constipation or diarrhea, nausea

Rifampin (150-600 mg/day)  
PXR agonist, lowers autotaxin  
- 10% risk of hepatitis usually occurring in the first 2 months

Naltrexone (12.5 to 50 mg/day)  
Opioid antagonist  
- Loss of appetite, irritability, GI side effects

Sertraline (25-100 mg/day)  
SSRI  
- Somnolence, nausea, dizziness, fatigue

AASLD and EASL guidelines 2009.
Refractory Itching

- **Nasobiliary drainage**\(^1\)
  - Significant improvement in itching, serum ALP and serum TB
  - Invasive, short duration of response (median 13 days)

- **UVB therapy**\(^2\)
  - Most patients had >60% reduction in itching
  - Time consuming: 3 sessions/wk, 60 sessions in total
  - Recurred in 25% after 11 months

- **Fibrates**\(^3\)
  - 46 pts with PBC and incomplete response to UDCA treated with bezafibrate 400 mg/day
  - 27 had itching at baseline, mean VAS 4.4
  - Itching disappeared in 17 pts, improved in 7 and was unchanged in 3 pts. Mean VAS at follow-up (29 mo): 0.8.

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Management of Itching Appearing During Treatment with Obeticholic Acid (OCA)

- Add cholestyramine. Allow 4 hours between use of OCA and that of bile acid binding resin

Alternatives:
- OCA dose reduction
- Temporary interruption of OCA (<14 days)
- Add antihistaminics

- Prefer cool environment (not dry)
- Use moisturizers
- Avoid hot showers
- Use loose clothes
- Avoid narcotics (can cause itching)
- Trim nails
- Use sun screen
Follow-up

- Discussed lifestyle changes
- Added cholestyramine 4g at bedtime; later had to increase to 2 packets/day
- Itching improved substantially – now it is 2 out of 10 in intensity
- Dose of OCA maintained at 10 mg/day, with normalization of ALP
THANK YOU!
For the most current information and clinically meaningful education on chronic liver diseases, please visit www.ChronicLiverDisease.org