Autoimmune Liver Diseases:
  Autoimmune Hepatitis (AIH)
  Primary Biliary Cholangitis (PBC)
  Primary Sclerosing Cholangitis (PSC)

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Disclosures

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Research Grants: Roche-Genentech, Novartis, Intercept, NGM, Gilead, CymaBay, Taiwan J

Scientific Advisory Boards: Roche-Genetech, Novartis, Intercept, Gilead

Off-Label Use of Drugs:
My presentation contains off-label use of FDA-approved medications as alternative therapies as recommended by current Practice Guidelines.
Autoimmune Liver Diseases

- Primary Biliary Cholangitis
- Primary Sclerosing Cholangitis
- Autoimmune Hepatitis
- IBD
  - UC >> CD
  - "colitis"
### Classic Autoimmunity and Autoimmune Liver Diseases

<table>
<thead>
<tr>
<th>Classic Autoimmunity</th>
<th>AIH</th>
<th>PBC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoantigen(s)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Female Predilection</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Autoimmune Genetics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Non-HLA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Environmental Factors</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Organ-specific Disease</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Associated Autoimmune Diseases</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Response to Immunosuppression</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Pathogenesis of Autoimmune Liver Diseases

- Complex Genetics
  - Negative Selection
  - HLA alleles-AutoAgs
  - Susceptibility
  - Disease progression

- Immune Repertoire

- Environmental Exposures
  - External (viruses, xenobiotics)
  - Internal (microbiome)

Immune Regulation

Autoimmune Liver Diseases
Autoimmune Hepatitis: A Progressive Disease

Causative factors
Immunogenetic, autoimmune, inflammatory

Environmental Triggers

↑ Serum ALT/AST

↑ Serum Bilirubin
At Diagnosis: Often Advanced Fibrosis or Cirrhosis

Healthy Liver

Portal Inflammation
Lymphoplasmacytic Interface Hepatitis

Hepatocellular Necroinflammation

Fibrosis

Cirrhosis

↑ ALT/AST; ANA, SMA, LKM1, Anit-SLA

↑ Bilirubin

↓ Alb, ↓ Plat, ↑ PT INR

Cirrhotic Liver
Autoimmune Hepatitis
Demographics and Epidemiology

- Rare disease, occurring globally in all races/ethnicities
- Female to male ratio = 3-4 to 1
- Afflicts both children and adults, including elderly
- Associated with extrahepatic AI and IMIDs
- Incidence varies among regions:
  - ~1.9 per 10^5 per year
  - Increasing worldwide
- Prevalence varies among regions: ~16.9 per 10^5
- 4-6% liver transplants in USA

Sahebjam F and Vierling JM Front Med, 2015
Vierling JM Clin Gastro Hepatol 2015
EASL Practice Guideline. J Hepatol; 2015
## Autoantibodies in Autoimmune Hepatitis

<table>
<thead>
<tr>
<th>AIH Type</th>
<th>AutoAbs</th>
<th>AutoAgs</th>
<th>Specificity Liver</th>
<th>Specificity AIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ANA</td>
<td>Histone/DNA</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>SMA</td>
<td>F-actin 50%</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>pANCA</td>
<td>β-tubulin</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>ASGPR</td>
<td>ASGPR</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>LKM1</td>
<td>CYP2D6</td>
<td>No</td>
<td>No (HCV infection)</td>
</tr>
<tr>
<td></td>
<td>LKM3</td>
<td>UGT1A</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>LC-1</td>
<td>FTCD</td>
<td>Yes</td>
<td>Yes, type 2</td>
</tr>
<tr>
<td></td>
<td>ASGPR</td>
<td>ASGPR</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>1 &amp; 2</td>
<td>SLA/LP</td>
<td>SepSecS protein</td>
<td>No</td>
<td>Yes (prognostic)</td>
</tr>
</tbody>
</table>

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Vierling JM Clin Gastro Hepatol 2015
Autoimmune Hepatitis: Disease-Specific Autoantigenic Epitopes

Type 1 AIH
- B Cell?
- CD4 T Cell?
- CD8 CTL?

Type 2 AIH
- CYP2D6 (8 epitopes)
  - B Cell
  - CD4 T Cell
  - CD8 CTL

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Vierling JM Clin Gastro Hepatol 2015
Autoimmune Hepatitis Histopathology
Three Key Features

A

B

C

Vierling JM Clin Gastro Hepatol 2015
Autoimmune Hepatitis
Revised Diagnostic Criteria of the International Autoimmune Hepatitis Group

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA</td>
<td>DR3 or DR4</td>
<td>+1</td>
</tr>
<tr>
<td>AP:AST (or ALT) ratio</td>
<td>&gt;3</td>
<td>-2</td>
</tr>
<tr>
<td></td>
<td>&lt;1.5</td>
<td>+2</td>
</tr>
<tr>
<td>Immune disease</td>
<td>Thyroiditis, colitis, others</td>
<td>+2</td>
</tr>
<tr>
<td>γ-globulin or IgG level above normal</td>
<td>&gt;2.0</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>1.5-2.0</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>1.0-1.5</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>&lt;1.0</td>
<td>0</td>
</tr>
<tr>
<td>Other markers</td>
<td>Anti-SLA, actin, LC1, pANCA</td>
<td>+2</td>
</tr>
<tr>
<td>ANA, SMA, or anti-LKM1 titers</td>
<td>&gt;1:80</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>1:80</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>1:40</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>&lt;1:40</td>
<td>0</td>
</tr>
<tr>
<td>Histological features</td>
<td>Interface hepatitis</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>Plasmacytic</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>Rosettes</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>None of above</td>
<td>-5</td>
</tr>
<tr>
<td></td>
<td>Biliary changes</td>
<td>-3</td>
</tr>
<tr>
<td></td>
<td>Other features</td>
<td>-3</td>
</tr>
<tr>
<td>AMA Positive</td>
<td>-4</td>
<td></td>
</tr>
<tr>
<td>Treatment response</td>
<td>Complete</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>Relapse</td>
<td>+3</td>
</tr>
<tr>
<td>Viral markers</td>
<td>Positive</td>
<td>-3</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>+3</td>
</tr>
<tr>
<td>Drugs</td>
<td>Yes</td>
<td>-4</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>+1</td>
</tr>
<tr>
<td>Pretreatment aggregate score:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite diagnosis</td>
<td>&gt;15</td>
<td></td>
</tr>
<tr>
<td>Probable diagnosis</td>
<td>10-15</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>&lt;25 g/day</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>&gt;60 g/day</td>
<td>-2</td>
</tr>
<tr>
<td>Post-treatment aggregate score:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite diagnosis</td>
<td>&gt;17</td>
<td></td>
</tr>
<tr>
<td>Probable diagnosis</td>
<td>12-17</td>
<td></td>
</tr>
</tbody>
</table>

**Autoimmune Hepatitis**

**Simplified Diagnostic Criteria of the International Autoimmune Hepatitis Group**

<table>
<thead>
<tr>
<th>Autoantibodies:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA or SMA ≥1:40</td>
<td>+1</td>
</tr>
<tr>
<td>≥1:80</td>
<td>+2</td>
</tr>
<tr>
<td>LKM-1 ≥1:40</td>
<td>+2</td>
</tr>
<tr>
<td>Anti-SLA Positive</td>
<td>+2</td>
</tr>
</tbody>
</table>

**Immunoglobulin Level**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG or &gt;ULN</td>
<td>+1</td>
</tr>
<tr>
<td>γ-globulin &gt;1.1 X ULN</td>
<td>+2</td>
</tr>
</tbody>
</table>

**Histological Features:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compatible with AIH</td>
<td>+1</td>
</tr>
<tr>
<td>Typical of AIH*</td>
<td>+2</td>
</tr>
</tbody>
</table>

**Absence of Viral Hepatitis:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>+2</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>

**Pretreatment Aggregate Score:**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite Diagnosis:</strong></td>
<td>≥7</td>
</tr>
<tr>
<td><strong>Probable Diagnosis:</strong></td>
<td>≥6</td>
</tr>
</tbody>
</table>


**Caveats:**

- Whenever “Probable” or “Non-diagnostic”, recalculate score using RDC!
- SDC better for classic cases
- RDC better for complex or unusual cases

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## 2010 AASLD Practice Guidelines in AIH: Stringent Criteria for Remission

<table>
<thead>
<tr>
<th>Goals</th>
<th>2010 AASLD Practice Guideline</th>
</tr>
</thead>
</table>
|       | 1. Prevent progression and need for OLT  
|       | 2. Minimize adverse events of immunosuppression |

<table>
<thead>
<tr>
<th>Biochemical Remission</th>
<th>Normalize:</th>
</tr>
</thead>
</table>
|                       | 1. ALT (<19 U/L females; <30 U/L males)  
|                       | 2. γ-globulin and IgG levels |

<table>
<thead>
<tr>
<th>Histologic Remission</th>
<th>Eliminate:</th>
</tr>
</thead>
</table>
|                       | 1. Interface hepatitis  
|                       | 2. Portal inflammatory infiltrates |

<table>
<thead>
<tr>
<th>Fibrosis</th>
<th>Prevent:</th>
</tr>
</thead>
</table>
|          | 1. Progression to cirrhosis  
|          | 2. Progression of existing cirrhosis to decompensation or increasing Child-Turcotte-Pugh and MELD scores |

| Immunosuppression | 1. Use combinations of immunosuppressive drugs to minimize adverse events caused by any single drug  
|                   | 2. Use alternative therapies as needed to achieve remission |

Differential Diagnostic Testing for Etiology of Acute or Chronic Liver Disease

RDC or SDC Scoring Indicate Probable or Definite Diagnosis of AIH

Choose Induction Immunosuppression

**Prednisone + Azathioprine**
- Week 1: 30 mg/d
- Week 2: 20 mg/d
- Week 3: 15 mg/d
- Week 4: 15 mg/d
- Maintenance: 10 mg/d

**Budesonide**
- 3 mg TID
  + **Azathioprine**
  - 1-2 mg/kg/d

**Prednisone Monotherapy**
- Week 1: 60 mg/d
- Week 2: 40 mg/d
- Week 3: 30 mg/d
- Week 4: 30 mg/d
- Maintenance: ≤20 mg/d

Non-cirrhotics only!

**Response**
- Maintenance
  - Taper Steroid
  - Continue Azathioprine

**Remission**
- Normal ALT, γ-globulin, IgG and Histology

**Withdraw Immunosuppression**

**Intolerance**
- Prednisone and/or Azathioprine

**Non-Response**
- Verify Compliance
  - Optimize Dosing

**Relapse**

**Remission Maintained**
- Monitor for Relapse

**Fail to Achieve Remission**

**Empiric Use of Alternative Therapies**
- MMF, MA, CSA, TAC, Sirolimus, Infliximab, Rituximab

**Vierling JM Clin Gastro Hepatol 2015**
Autoimmune Hepatitis
Relapse of AIH After Withdrawal of Therapy
Increased Probability of Cirrhosis and Need for OLT

Autoimmune Hepatitis: Alternative Immunosuppressive Therapies

- **Calcineurin Inhibitors**
  - Cyclosporine
  - Tacrolimus

- **Proliferation Inhibitors**
  - Mycophenolic acid

- **CD20+ B Cell Depletion**
  - Rituximab

- **mTOR Inhibitors**
  - Sirolimus
  - Everolimus

- **TNF-α Inhibitors**
  - Infliximab
  - Adalimumab
Autoimmune Hepatitis: Natural Immunosuppressive in Pregnancy

- Pre-Implantation Factor:
  - Secreted by embryo
  - Creates maternal immune tolerance
  - Recombinant peptide completed phase 1b clinical trial in refractory AIH

Cholestatic Variants or “Overlap Syndromes”
AIH-PSC and AIH-PBC

Diagnostic Criteria Based on Disease-Specific Pathogenesis Urgently Needed!

Patterns of Presentation:
- PSC → AIH (adults)
- AIH → PSC (children>adults)
- PSC + AIH (children)

AIH Component Responsive to Immunosuppression:
- Corticosteroid
- Azathioprine

PBC or PSC Component:
- Consider UDCA

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Autoimmune Liver Diseases
Excellent Survivals Post-OLT UNOS Database

Evaluate for OLT:
- MELD Score ≥ 15
- Life Threatening Complications
- HCC

Allograft Loss After OLT
Impact of Recurrent Autoimmune Diseases

Autoimmune Hepatitis 2016
Key Points

- Increasing incidence globally
- Complex immunogenetics: HLA DR3/DR4 alleles >>> Multiple AI/IMID SNPs
- Diagnosis: exclusion of viral, drug-induced, metabolic and genetic diseases
- Revised Diagnostic and Simplified Diagnostic Criteria: Diagnostic Aids
- Remission based on 2010 AASLD Practice Guideline:
  - Normalization of ALT
  - Normalization of IgG/γ-globulin
  - Elimination of interface hepatitis and portal inflammation
- Remission less common using stringent 2010 AASLD definition
- Disease-specific diagnostic criteria for Overlap Syndromes needed
- Alternative immunosuppression for non-response or intolerance to steroids and/or azathioprine
- OLT evaluation for cirrhotics with MELD ≥ 15 or HCC
Anatomic Factors in Biliary Diseases

- Each bile duct accompanied by a branch of the hepatic artery of equal caliber
- Each bile duct surrounded by a peribiliary capillary plexus from the hepatic artery
- Hepatic Lymph from Space of Disse flows retrograde in peribiliary lymphatics
Primary Biliary Cholangitis: A Progressive Disease

Causative factors
- Genetic/autoimmune,
- inflammatory, LPS
- Environmental Triggers

Healthy Liver
- AMA +
  - ↑ Serum ALP
  - Diagnostic/prognostic
  - ↑ AST, ALT, GGT
  - ↑ Bilirubin
  - Prognostic

Cirrhotic Liver
- ↓ Albumin, ↓ Platelets

↑ Serum ALP
Hepatocellular damage
Inflammation
Fibrosis
Cirrhosis

Cholangitis
Cholestatics
(bile acid toxicity)
Time for a Name Change!
Primary Biliary Cirrhosis to Cholangitis

SPECIAL ARTICLE

Changing Nomenclature for PBC: From ‘Cirrhosis’ to ‘Cholangitis’

Ulrich Beuers,1 M. Eric Gershwin,2 Robert G. Gish,3 Pietro Invernizzi,4 David E.J. Jones,5 Keith Lindor,6 Xiong Ma,7 Ian R. Mackay,8 Albert Parés,9 Atsushi Tanaka,10 John M. Vierling,11 and Raoul Poupon12

2015; Gut, Gastroenterology, J Hepatol, Clin Gastroenterology Hepatol, Am J Gastroenterol, Dig Liver Dis
Primary Biliary Cholangitis
Demographics and Epidemiology

- Rare disease, occurring globally in all races/ethnicities
- Female to male ratio = 10-11 to 1
- Afflicts adults, but not children
- Associated with extrahepatic AI and IMIDs
- Incidence incomplete globally: 60 per 10^6/year Europe/USA
- Prevalence incomplete globally: 350 per 10^6 Europe/USA
- ≤ 10% liver transplants in USA

Primary Biliary Cholangitis

- Adult woman (mostly ≥40 years of age)
- Cholestatic pattern of liver tests (Alk Phos, ggt)
- AMA-Positive
- Compatible liver histology
- Absence of biliary tract dilation on imaging

Diagnostic Criteria: 2 of 3
Primary Biliary Cholangitis
Autoantibodies and Disease Specificity

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• AMA</td>
<td>95-98</td>
</tr>
<tr>
<td>• ANA</td>
<td>5-54</td>
</tr>
<tr>
<td>• gp210</td>
<td>26</td>
</tr>
<tr>
<td>- Promyelocytic leukemia protein</td>
<td>19</td>
</tr>
<tr>
<td>• Sp100</td>
<td>21</td>
</tr>
<tr>
<td>- Laminin B receptor</td>
<td>1</td>
</tr>
<tr>
<td>- p62</td>
<td>25</td>
</tr>
<tr>
<td>- SOX13</td>
<td>10-15</td>
</tr>
<tr>
<td>- sp140</td>
<td>15%</td>
</tr>
<tr>
<td>• SMA</td>
<td>26-49</td>
</tr>
<tr>
<td>• RF</td>
<td>24-60</td>
</tr>
<tr>
<td>• Thyroid</td>
<td>15-26</td>
</tr>
</tbody>
</table>
Primary Biliary Cholangitis
PDC-E2-Specific Autoepitopes: Shared aa Motif

B Cells

CD4 and CD8 T Cells
Primary Biliary Cholangitis
Bile Ductular Reaction and Unique Biliary Cirrhosis

Bile Ductular Reaction

Biliary Cirrhosis (Jig Saw Puzzle)
Histopathological Progression of PBC

Therapeutic Strategies for Parallel Pathogenic Mechanisms in PBC

PBC-Specific
- Inflammation → NSCD
- NSCD Granulomas

Clinical & Experimental Biliary Obstruction
- Ductular Reaction
- Interface → Hepatitis
- Stellate → Fibrosis
- Biliary Cirrhosis

Ductopenic Biliary Obstruction

Immune-Mediated NSDC
- Biliary Ischemia; Bile leakage
- ↓ Cholangiohepatic circulation

Progression
Primary Biliary Cholangitis: UDCA as Monotherapy

Bile Acids

UDCA
Biochemical Response to UDCA at 1 Year Predicts Disease Progression

Corpechot et al. Hepatology 2008
Dichotomous ALP and Bilirubin Predict Survival

**Alkaline Phosphatase (ALP)**
- ALP ≤1.67 xULN
  - Survival: 297/1991
- ALP >1.67 xULN
  - Survival: 395/1258

**Bilirubin**
- Normal bilirubin
  - Survival: 416/2941
- Abnormal bilirubin
  - Survival: 418/740

Hazard Ratio:
- ALP >1.67 vs ≤1.67 = 2.2 (1.9-2.5)
- Abnormal vs normal bili = 5.1 (4.3-5.9)

Courtesy of Global PBC Study Group
Primary Biliary Cholangitis: Predictive Significance of Combining ALP and Bilirubin

Global PBC Group (N=4845)

- **Normal Bilirubin**
  - ALP ≤1.67xULN: 202/1658
  - ALP >1.67xULN: 155/827
  - Survival:
    - Follow-up (Years): 0, 5, 10, 15
    - 100%, 80%, 60%, 40%, 20%, 0% survival
- **Abnormal Bilirubin**
  - ALP ≤1.67xULN: 76/180
  - ALP >1.67xULN: 226/360
  - Survival:
    - Follow-up (Years): 0, 5, 10, 15
    - 100%, 80%, 60%, 40%, 20%, 0% survival

UK-PBC (N=4022)

- **Normal Bilirubin**
  - Survival:
    - Follow-up (Years): 0, 5, 10, 15
    - 100%, 80%, 60%, 40%, 20%, 0% survival
- **Abnormal Bilirubin**
  - Survival:
    - Follow-up (Years): 0, 5, 10, 15
    - 100%, 80%, 60%, 40%, 20%, 0% survival

Courtesy of Global PBC Study Group and UK-PBC
Outcomes in PBC Patients Taking UDCA

GLOBE Score

GLOBE Score ≤30

GLOBE Score >30

\[ GS = 0.44378 \times \text{age at start of UDCA} + 0.93982 \times \ln(\text{Bili} \times \text{ULN at 1 yr F/U}) + 0.335648 \times \ln(\text{ALP} \times \text{ULN at 1 yr F/U}) - 2.266708 \times \text{Alb} \times \text{LLN at 1 yr F/U} - 0.002581 \times \text{Plts/10^9/L at 1 yr F/U} \]

Trends in OLT for PBC and PSC
Indication for OLT Reduced in PBC After UDCA

Lee et al. J Clin Gastroenterol Hepatol 2007; 5:1313
PBC-AIH Overlap Syndrome
Infrequent but Indicator of Progressive Disease

Primary Biliary Cholangitis: Imminent Therapy

- Bile Acids
- UDCA
- FXR Agonist
- Obeticholic Acid
FXR: Central Roles in Multiple Pathways

**FIBROSIS**
- ↓Stellate cell activation (α-SMA)
- ↑Stellate cell apoptosis (TIMP-1)
- ↓Fibrogenesis (TGF-β1)
- ↑Matrix degradation (MMP-2)

**INFLAMMATION**
- ↓NF-κB
- ↓TNFα, IL-1β, IL-17, IFN-γ
- ↓CRP

**ATHEROSCLEROSIS**
- ↑Vasodilation (eNOS)
- ↓Inflammation (COX-2, iNOS)
- ↓Calcification (JNK)
- ↓Smooth muscle cell migration

**LIPID METABOLISM**
- ↓Triglyceride synthesis (SREBP-1c)
- ↑Triglyceride clearance (apoC-III)
- ↓HDL-C (SR-B1, CETP)
- ↑LDL-C (CETP)

**GLUCOSE METABOLISM**
- ↑Insulin signaling (FGF19)
- ↑Insulin sensitivity (IRS-1, IRS-2)
- ↑Insulin production (KLF11, GLUT-2)
- ↓Hepatic gluconeogenesis (PEPCK)

**BILE ACID HOMEOSTASIS**
- ↓Bile acid synthesis (CYP7A1)
- ↓Bile acid uptake (NTCP)
- ↑Bile acid secretion (BSEP)
- ↓Bile acid absorption (ASBT)

*In vitro/in vivo* studies do not necessarily correlate with clinical response.
An open label extension followed the double blind period; UDCA=Ursodeoxycholic acid; ALP=Alkaline phosphatase; ULN=Upper limit of normal
POISE Phase 3 Trial
Randomized, Placebo-Controlled Trial of OCA in PBC
Primary Endpoint:
Proportion of patients achieving ALP <1.67x ULN with bilirubin ≤ULN and ≥15% reduction in ALP. * p<0.0001 vs. placebo

*Titration OCA group: 5 mg OCA for 6 months →10 mg OCA if well tolerated & ALP >1.67x ULN or bilirubin >ULN

Phase 3 POISE Trial
Changes in Liver Chemistry (N=216)


**Titration OCA group:** 5 mg OCA for 6 months → 10 mg OCA if well tolerated & ALP >1.67x ULN or bilirubin >ULN
Improvement in Inflammatory Markers Month 12

Placebo (N=73)  
OCA Titration ± UDCA (N=70)  
OCA 10 mg ± UDCA (N=73)

**Median (∆±IQR) from Baseline**

- **IgM (g/L)**
- **TNF-α (pg/mL)**
- **IL-12 (pg/mL)**
- **hsCRP (mg/L)**

* **p<0.05,  ** **p<0.01,  *** **p<0.0001

IQR=Interquartile range; Titration OCA group: 5 mg OCA for 6 months then titrated to 10 mg OCA if tolerated & ALP ≥1.67x ULN or <15% reduction in ALP or bilirubin >ULN.

Phase 3 POISE trial
Changes in lipids from baseline at 6 and 12 months (n=216)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=73)</th>
<th>Titration OCA (n=70)</th>
<th>10 mg OCA (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HDL (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>-0.6</td>
<td>-0.4</td>
<td>-0.2</td>
</tr>
<tr>
<td>12 months</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>LDL (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>-0.6</td>
<td>-0.4</td>
<td>-0.2</td>
</tr>
<tr>
<td>12 months</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>VLDL (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>-0.6</td>
<td>-0.4</td>
<td>-0.2</td>
</tr>
<tr>
<td>12 months</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>-0.6</td>
<td>-0.4</td>
<td>-0.2</td>
</tr>
<tr>
<td>12 months</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Titration OCA group: 5mg OCA for 6 months then titrated to 10mg OCA if well tolerated & ALP ≥1.67x ULN or bilirubin >ULN

# Phase 3 POISE Trial
## Frequent AEs (≥5%)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=73)</th>
<th>Titration OCA (n=70)</th>
<th>10 mg OCA (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Pruritus</strong></td>
<td>28 (38%)</td>
<td>39 (56%)</td>
<td>50 (68%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (14%)</td>
<td>11 (16%)</td>
<td>17 (23%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>13 (18%)</td>
<td>17 (24%)</td>
<td>13 (18%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (12%)</td>
<td>4 (6%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8 (11%)</td>
<td>2 (3%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (4%)</td>
<td>4 (6%)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (18%)</td>
<td>12 (17%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>1 (1%)</td>
<td>5 (7%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Cough</td>
<td>5 (7%)</td>
<td>4 (6%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (5%)</td>
<td>5 (7%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>4 (5%)</td>
<td>5 (7%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>5 (7%)</td>
<td>5 (7%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>8 (11%)</td>
<td>4 (6%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>8 (11%)</td>
<td>4 (6%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8 (11%)</td>
<td>4 (6%)</td>
<td>4 (5%)</td>
</tr>
</tbody>
</table>

POISE LTSE with Placebo Cross-Over

Alkaline Phosphatase (ALP)

Bilirubin

Double-Blind Phase
Randomized Treatment

Open-Label Phase
All Receive OCA

Placebo ± UDCA
OCA 5-10 mg Titration ± UDCA

10 mg OCA ± UDCA

Double-Blind Phase
Randomized Treatment

Open-Label Phase
All Receive OCA

Placebo, n
73 69 71 69 70 64 60 56 24

Titation, n
70 69 69 66 64 63 62 54 25

10 mg OCA, n
73 69 64 64 62 64 59 54 25

Courtesy of Intercept Pharmaceuticals
PBC: Alternative and Future Therapies

**Anti-Retrovirals**

- UDCA + PPARα Agonists
  - Fenofibrate (α)
  - Bezafibrate (α>γ/δ)

**Non-Specific Immunosuppression**
- Prednisolone
- Budesonide + UDCA

**Targeted Immunologic**
- Anti-TNFα
- Anti-CD20 (Rituximab)
- CTLA-4 Ig (Abetacept)
- Anti-CXCL-10 (MDX-1100) (NI-08091)
- Anti-IL-12 (Ustekinumab)
- Tregs

**Bile Acids**
- UDCA
- FK506

**FXR Agonist**
- Obeticholic Acid

**UDCA + PPARα Agonists**

**FGF19 (NGM282)**
Primary Biliary Cholangitis 2016
Key Points

- Rare disease with new name
- Complex immunogenetics
- Diagnosis: ALP (ggt), AMA, compatible histology
- Response to UDCA in majority: ↑ OLT free survival
- Unmet therapeutic need UDCA non-response or intolerance
- Clinical trials reliant on surrogate primary endpoints:
  - ALP ≤ 1.67X ULN
  - Bilirubin WNL
- FXR agonist Obeticholic Acid met phase III trial primary and secondary endpoints (FDA Advisory Board, April 2016)
- Alternative therapeutic targets under investigation
- OLT evaluation for cirrhotics with MELD ≥ 15 or HCC
Primary Sclerosing Cholangitis

Vierling JM: Primary Sclerosing Cholangitis. Schiff's Liver Diseases, 12th Ed, 2017
Primary Sclerosing Cholangitis
Definition

Chronic, progressive, cholestatic, putatively autoimmune disease characterized by:

- Segmental fibrosing inflammation of intra- and/or extra-hepatic bile ducts
- Fibrous obliterative cholangitis → ductopenia
- Interface hepatitis
- Progression to biliary cirrhosis

Premalignant Disease associated with risks for:

- Cholangiocarcinoma
- Colorectal carcinoma in ulcerative colitis
- Gallbladder carcinoma
- Hepatocellular carcinoma rare in cirrhotics
Primary Sclerosing Cholangitis
Epidemiology and Demographics

**Epidemiology**
- Afflicts all ages and races
- Prevalence ~ 40 per million with familial predisposition
  - 0.7% among 1st degree relatives (100-fold ↑)
  - 1.5% among siblings
- Male: Female Ratio: 1.5:1 (60% males)
- Diagnosis < 45 years of age in 67%

**Association with IBD**
- Ulcerative colitis: 70-98%, but with unique features
  - Rectal sparing (52% vs 6%)
  - Backwash ileitis 51% vs 7%)
  - 5 yr cumulative incidence of colorectal ca:
    - 33% vs 13% (p=0.054)
- Crohn’s colitis or ileocolitis: 3-13%
Cancers

PSC

Autoimmune Diseases

IBD
UC>>CD
“colitis”

PSC Disease Associations
Primary Sclerosing Cholangitis: Diagnostic Algorithm

Cholestatic Liver Test Profile
- Chronically Elevated ALP and ggt or 5'NT Confirming Hepatobiliary Origin
- R Ratio < 2

Mixed Cholestatic-Hepatocellular Profile
- Chronically Elevated ALP and ggt or 5'NT Confirming Hepatobiliary Origin
- R Ratio 2-5

Normal Liver Test Panel
- Imaging with Incidental Finding of Biliary Tract Dilation(s)
- Chronic Elevations of ggt without Identifiable Cause

MRCP

- Multifocal Bile Duct Strictures and Segmental Dilations
- Exclude Causes of SSC (Diagnostic Liver Biopsy if Clinically Indicated)

- Classic PSC
  - Clinical IBD?
    - Yes: Annual Surveillance Colonoscopy to Detect Dysplasia and/or Aneuploidy in UC
    - No: Monitor for Future Symptoms of IBD

- Surveillance for CCA

- Indeterminate or No Evidence of Multifocal Bile Duct Strictures and Segmental Dilations
- ERCP
- No Cholangiographic Evidence of Multifocal Bile Duct Strictures and Segmental Dilations
- Liver Biopsy to Assess for Small Duct PSC

- Small Duct PSC
  - Small Duct PSC
  - No Small Duct PSC

- Monitor for Progression
- Pursue Other Diagnoses

Vierling JM: Primary Sclerosing Cholangitis. Schiff’s Liver Diseases, 12th Ed, 2017
Advances in Cholangiographic Detection of PSC Strictures

* Long stricture worrisome for CCA

Images courtesy of Dr. B Banarjee, Perspectum Diagnostics, Ltd

Vierling JM: Primary Sclerosing Cholangitis. Schiff's Liver Diseases, 12th Ed, 2017
Small Ducts

Pathology of PSC

Medium Ducts

Images Courtesy of: Dr. S Dhinra; Vierling JM: Primary Sclerosing Cholangitis. Schiff’s Liver Diseases, 12th Ed, 2017
PBC and PSC
Bile Ductular Reaction Results in Biliary Cirrhosis

Bile Ductular Reaction

Biliary Cirrhosis (Jig Saw Puzzle)
## PSC Association with Multiple Autoantibodies

<table>
<thead>
<tr>
<th>Studies (n=)</th>
<th>Antibody</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>pANCA</td>
<td>33-88% (&gt;65%)</td>
</tr>
<tr>
<td>6</td>
<td>ANA</td>
<td>7-77% (35%)</td>
</tr>
<tr>
<td>3</td>
<td>SMA</td>
<td>13-20%</td>
</tr>
<tr>
<td>3</td>
<td>AMA</td>
<td>0-9%</td>
</tr>
<tr>
<td>1</td>
<td>Anti-colon</td>
<td>62%</td>
</tr>
<tr>
<td>2</td>
<td>Anti-colon protein (Mr 40kDa)</td>
<td>67%</td>
</tr>
<tr>
<td>1</td>
<td>Anti-endothelial cell</td>
<td>35%</td>
</tr>
<tr>
<td>6</td>
<td>Miscellaneous</td>
<td>4-66%</td>
</tr>
</tbody>
</table>

Primary Sclerosing Cholangitis
pANCA, Atypical pANCA (pANNA) and cANCA

PSC and Ulcerative Colitis
Cumulative Risk of Colorectal Carcinoma

Primary Sclerosing Cholangitis
Incidence of Cholangiocarcinoma

**Important Conclusions:**

1. CCA diagnosis clusters within 24 months of initial diagnosis of PSC
2. Long-term incidence 0.5-1.5% per year
3. CCA not inevitable in PSC

Cumulative incidence of cholangiocarcinoma (%) vs. Years since PSC diagnosis

Sensitivity and Specificity of CA-19-9 for CCA in PSC

Cholangiocarcinoma
Fluorescence In Situ Hybridization (FISH)

chrom 3 = red, chrom 7 = green, chrom 17 = aqua, locus 9p21 = gold

Normal

Polysomy

2 signals per color

> 2 signals per color
# Surveillance Strategies: CRC, CCA and Gallbladder Adenocarcinoma

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Imaging and/or Endoscopy</th>
<th>Laboratory Testing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colorectal carcinoma</strong></td>
<td>Annual Colonoscopy</td>
<td>CEA</td>
<td>4 quadrant biopsies every 10 cm cecum to anus to assess for both aneuploidy &amp; dysplasia</td>
</tr>
<tr>
<td><strong>Cholangiocarcinoma</strong></td>
<td>Annual MRCP, ERC &amp; cholangioscopic biopsies of suspicious strictures</td>
<td>CA-19-9 semiannually (only ABO Lewis Ag+) CEA?</td>
<td>FISH aneuploidy analysis required CA-19-9: false+ elevations with cholangitis or non-malignant obstruction</td>
</tr>
<tr>
<td><strong>Gallbladder carcinoma</strong></td>
<td>Annual US or cross-sectional imaging</td>
<td>No defined or exploratory biomarkers</td>
<td>High suspicion for any polyp, especially if enlarging. Inappropriate to observe until 1 cm dia</td>
</tr>
</tbody>
</table>

Vierling JM: Primary Sclerosing Cholangitis. Schiff’s Liver Diseases, 12th Ed, 2017
Small Duct PSC:
- 5-10% of PSC
- Normal M(E)RCP
- Biopsy required
- No risk of CCA
- Progresses to classic PSC in <30%
- NOT Early Phase of PSC

Primary Sclerosing Cholangitis (PSC): A Complex Progressive, Cholestatic Disease of Unknown Etiology

Vierling JM: Primary Sclerosing Cholangitis. Schiff’s Liver Diseases, 12th Ed, 2017
Primary Sclerosing Cholangitis
UDCA Does Not Prevent Dominant Strictures

Development of Dominant Strictures

Endoscopic Therapies:
• Dilation alone superior
• Dilation + Stent
  • ↑ infections?
  • Obstruction
  • Replacement

Endoscopic Diagnostics
• Cholangioscopic biopsy
• Brush cytology

Primary Sclerosing Cholangitis
Poor Response to Immunosuppressive Therapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-penicillamine</td>
<td>Ineffective</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Occasional benefit*</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Modest and variable</td>
</tr>
<tr>
<td>Prednisone + Colchicine</td>
<td>Ineffective</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Ineffective</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Ineffective</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Occasional benefit</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Biochemical improvement</td>
</tr>
<tr>
<td>Pentoxyfyline</td>
<td>Ineffective</td>
</tr>
<tr>
<td>Entercept</td>
<td>Ineffective</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Ineffective</td>
</tr>
</tbody>
</table>

*budesonide
Primary Sclerosing Cholangitis
Response to Immunosuppressive Therapy

- ↑ serum IgG4 or ↑ tissue IgG4+ B cells
- “Autoimmune” Secondary Sclerosing Cholangitis
- More severe outcomes:
  - Worse cholestasis
  - Rapid progression to LRD or OLT
  - Rapid development of colorectal ca
- Responsive to Immunosuppression?
  - Corticosteroids
  - Azathioprine

Overlap Syndrome
PSC and Autoimmune Hepatitis

Patterns of Presentation
- PSC → AIH (adults)
- AIH → PSC (children)
- PSC + AIH (children)

AIH Component Responsive to Immunosuppression:
- Corticosteroid
- Azathioprine
- Other?
Primary Sclerosing Cholangitis: Current and Future Therapies

UDCA

Bile Acids

No! AASLD

Maybe! EASL

Dose?

UDCA
Primary Sclerosing Cholangitis
Physiological Dosing of UDCA

Percentage of UDCA in biliary bile acids

- No differences with or without IBD
- Study of UDCA biliary enrichment in patients after colectomy and ileoanal pouch:
  - Normal in 5 of 7
  - Reduced in 2

Primary Sclerosing Cholangitis
Efficacy of UDCA Therapy

• Randomized, Placebo Controlled Trial  n= 105
• UDCA 13-15 mg/kg/d (n= 51) vs Placebo (n= 51)
• Primary End Points: Time to Treatment Failure (death, OLT, histological progression, varices, ascites, encephalopathy, quadrupling of bilirubin, worsening fatigue

Lindor KD, et al: NEJM 1997; 336: 691-95
Primary Sclerosing Cholangitis
High Dose UDCA Superior to Placebo for 24 Months

NIH NIDDK High Dose UDCA* for PSC Model of All Primary Endpoints
Adjusted for Mayo Risk Score, Presence of Varices and Stage

* UDCA 28-32 mg/kg/d; Lindor KD, et al. Hepatology 2009; 50: 808-815
Primary Sclerosing Cholangitis
Efficacy of UDCA Therapy

• Randomized, Double-Blind, Placebo Controlled Trial  \( n = 219 \)
• UDCA 17-23 mg/kg/d (\( n = 110 \)) vs Placebo (\( n = 109 \))
• Primary End Point: 50% Improvement in Survival (Death or OLT)

PSC: Kaplan-Meier Analysis of Survival in UDCA Treated Patients

Prognosis of PSC Treated with UDCA
Positive Effect of ALP Normalization

Ursodeoxycholic Acid (UDCA) Therapy in PSC

**Inclusion Criteria**
- Diagnosis of Classic PSC
- ALP ≥ 1.5 x ULN
- Pre-Cirrhotic or
- CTP Class A Cirrhosis

**Exclusion Criteria**
- Diagnosis of Small Duct PSC
- CTP Class B or C Cirrhosis
- Untreated Dominant Stricture
- Suspicion of CCA

Interest in Exploring Clinical Therapeutic Trials for PSC

Refer to Clinical Trial Center

Discuss Risks and Benefits of Empiric Therapy with UDCA 17-23 mg/kg/day

Discuss Eligibility for Clinical Therapeutic Trials for PSC

Execute Informed Consent

Enroll in Clinical Therapeutic Trial for PSC

Discuss Rountine Follow-Up and Surveillance

Continue Routine Follow-Up and Surveillance

Discontinue UDCA

Continue Follow-Up and Surveillance

Await Novel Therapies

Vierling JM: Primary Sclerosing Cholangitis. Schiff’s Liver Diseases, 12th Ed, 2017
UDCA and Risk of Colorectal Neoplasia in Patients with PSC-IBD

UDCA and Risk of Advanced Colorectal Neoplasia in Patients with PSC-IBD

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braden 2012</td>
<td>1.420</td>
<td>0.067</td>
<td>30.246</td>
</tr>
<tr>
<td>Eaton 2011</td>
<td>1.261</td>
<td>0.165</td>
<td>9.648</td>
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<tr>
<td>Lindstrom 2012</td>
<td>0.326</td>
<td>0.033</td>
<td>3.254</td>
</tr>
<tr>
<td>Pardi 2003</td>
<td>0.146</td>
<td>0.007</td>
<td>3.193</td>
</tr>
<tr>
<td>Wolf 2005</td>
<td>0.616</td>
<td>0.165</td>
<td>2.304</td>
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<tr>
<td>Tung 2001</td>
<td>0.099</td>
<td>0.022</td>
<td>0.442</td>
</tr>
<tr>
<td>Ullman 2003</td>
<td>0.233</td>
<td>0.038</td>
<td>1.429</td>
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<tr>
<td></td>
<td>0.349</td>
<td>0.167</td>
<td>0.729</td>
</tr>
</tbody>
</table>

PSC: Alternative and Future Therapies

- Bile Acids
  - UDCA
  - FXR Agonist
    - Obeticholic Acid

Anti-Fibrotics:
- Simtuzumab
- mTOR inhibitors
- Galectin?

Phase II Initiated

FGF19 (NGM282)
Medical Management of PSC Dependent on Stage of Disease Progression

Vierling JM: Primary Sclerosing Cholangitis. Schiff's Liver Diseases, 12th Ed, 2017
Autoimmune Liver Diseases
Excellent Survivals Post-OLT UNOS Database

Evaluate for OLT:
- MELD Score ≥ 15
- Life Threatening Complications
- HCC

AILDs
~ 26%

PBC
~12%
PSC, AIH, All Other
~ 8%~ 6%* ~ 74%

Patient Survival (%)

- Recurrent PBC in ~30%
- Little effect on graft or patient survivals

Primary Sclerosing Cholangitis
Survival after OLT for PSC and Malignancy

OLT for Autoimmune Liver Diseases
Recurrence in Allograft

Schreuder et al. Transplant Int. 2009; 22:144
Recurrent PSC after OLT
Protective Effect of Colectomy

Vera A et al., Lancet 2002
Cholangiocarcinoma Treatment Protocol

- External beam radiation
- Brachytherapy
- Staging Laparotomy
- Capecitabine
- Liver transplantation
Liver Transplantation for Cholangiocarcinoma
Survival 1993-2007

Survival (%) vs. Years after transplantation

N= 81

72 ± 7%
PSC 2017: Key Points

- Rare disease, strongly associated with IBD (UC>>CD), male sex, AI genetics
- Diagnosis:
  - Cholestatic liver tests: ALP (ggt), pANNA (68%)
  - Cholangiography: MRCP or ERCP
  - Liver biopsy for small duct PSC; non-invasive fibrosis staging
  - IgG4-SSC in up to 10% previously diagnosed
- Premalignant disease:: CCA, CRC in IBD, Gallbladder ca, HCC in cirrhotics
  - PSC independent risk for CRC in IBD and accelerates kinetics
  - CCA not inevitable; screening cholangioscopy + aneuploidy/dysplasia testing
  - Regard all gallbladder polyps as malignant
- UDCA controversy: Low and High Doses vs 17-25 mg/kg/d safe but efficacious in minority
- Highest survival with normalization of ALP (spontaneously or with UDCA)
- Dominant strictures → dilation without stenting
- Clinical trials reliant on surrogate primary endpoints: ALP, ggt, bili, MRCP, biopsy
- OLT for cirrhotics with MELD ≥ 15 or HCC; UNOS protocol for CCA
Thank You!