Overview of Autoimmune Liver Diseases

John M Vierling, MD, FACP, FAASLD, AGAF
Professor Medicine and Surgery
Chief of Hepatology
Director of Advanced Liver Therapies
Baylor College of Medicine
Baylor St. Luke’s Medical Center
Houston, Texas
Research Grants: Arena, CymaBay, Enanta, Genfit, Genkyotex, Gilead, Intercept, Lilly, NGM Biopharmaceuticals, Novartis, Roche-Genentech

Scientific Advisor: Arena, Gilead, Lilly, Intercept, Novartis, Roche Genentech

Off-Label Use of Drugs: Discussion of off-label use of FDA-approved medications as therapies based on published data and recommendations of current Practice Guidelines.
Primary Biliary Cholangitis
Diagnostic Criteria

- Cholestatic pattern of liver tests (Alk Phos, ggt)
- AMA-Positive
- Compatible liver histology
- Absence of biliary tract dilation on imaging
Primary Biliary Cholangitis
PBC-Specific Autoantibodies: AMA and ANA

<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>- Lamin 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
Clinicopathological Progression

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
<th>Compensated</th>
<th>Decompensated</th>
</tr>
</thead>
<tbody>
<tr>
<td>- AMA +</td>
<td>- AMA +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ALP, ggt WNL</td>
<td>↑ ALP, ALT/AST with later ↑ Bilirubin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Dickson R. Prog Liver Dis, 1998.
Primary Biliary Cholangitis: Predictive Significance of ALP and Bilirubin in UDCA Era

Global PBC Group (N=4845)

Survival (%)

Follow-up (Years)

ALP ≤1.67xULN

ALP >1.67xULN

Normal Bilirubin

202/1658

155/827

p=0.00015

Abnormal Bilirubin

76/180

226/360

p=0.00086

UK-PBC (N=4022)

Survival (%)

Follow-up (Years)

ALP ≤1.67xULN

ALP >1.67xULN

Normal Bilirubin

Abnormal Bilirubin

p=0.00015

p=0.00086

Courtesy of Global PBC Study Group and UK-PBC
Efficacy of UDCA Treatment of PBC: Better Event-Free Survival in Earlier Stages of Disease

Survival on UDCA is inversely related to stage of PBC when treatment initiated:
- Survival of patients with early-stage PBC comparable to survival of the general population ($p=0.254$)
- Survival in advanced-stage PBC significantly worse ($p<0.001$)

Primary Biliary Cholangitis: GLOBE Score: Survival Benefit of UDCA Treatment

GLOBE Score Calculation:

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

Primary Biliary Cholangitis:
Response to UDCA Reveals Magnitude of Unmet Need

- **PBC**
  - **UDCA**
    - **Responders**: 60%
      - Reduced Liver-related Deaths or OLT
    - **Nonresponders**: 40%
      - Progression
        - Cirrhosis, PHTN and/or HCC
        - Death or OLT

Obeticholic Acid
Modified Bile Acid and Potent FXR Agonist

FXR= Farnesoid X Nuclear Receptor
Natural ligand chenodeoxycholic acid
OCA 100X greater FXR agonist

## Primary Biliary Cholangitis: POISE RCT
### Adverse Events of Obeticholic Acid (OCA) Therapy

**Adverse Events Occurring in ≥10% of Subjects**

<table>
<thead>
<tr>
<th>Event</th>
<th>Double-Blind Phase</th>
<th></th>
<th></th>
<th>Open-Label Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 73)</td>
<td>Obeticholic Acid, 5–10 mg (N = 70)</td>
<td>Obeticholic Acid, 10 mg (N = 73)</td>
<td>Total Obeticholic Acid (N = 193)</td>
</tr>
<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>
</tbody>
</table>

Obeticholic Acid for Decompensated Cirrhosis
FDA Boxed Warning for OCA (OCALIVA)

Staging / Classification | Non-Cirrhotic or Compensated Child-Pugh Class A | Child-Pugh Class B or C or Patients with a Prior Decompensation Event<sup>a</sup>
--- | --- | ---
Starting OCALIVA Dosage for first 3 months | 5 mg once daily | 5 mg once weekly
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<sup>b</sup> | 10 mg once daily | 5 mg twice weekly (at least 3 days apart)  
Titrate to 10 mg twice weekly (at least 3 days apart) based on response and tolerability
Maximum OCALIVA Dosage | 10 mg once daily | 10 mg twice weekly (at least 3 days apart)

<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

[https://www.fda.gov/drugs/drugsafety/ucm594941.htm](https://www.fda.gov/drugs/drugsafety/ucm594941.htm) (accessed 27 FEB 2018)
# Primary Biliary Cholangitis

## Management of Cholestatic Pruritus

### General Recommendations
- Skin moisturizer
- Wet, cooling, or moist wraps
- Topical agents with symptomatic relief (eg, camphor, menthol)
- Relaxation techniques
- Training to stop the cycle of itch, scratch, itch

### First-line
- Bile acid sequestrants:
  - Cholestyramine
  - Colestipol, colesvelam

### The following agents may be used for pruritus refractory to bile acid sequestrants:

#### Second-line
- Rifampicin

#### Third-line
- Oral opioid antagonists:
  - Naltrexone
  - Nalmefene

#### Fourth-line
- Selective serotonin reuptake inhibitors:
  - Sertraline

---

### Primary Biliary Cholangitis

**Management of Complications of Cholestasis/Cirrhosis**

<table>
<thead>
<tr>
<th>Complications of Cholestasis or Cirrhosis</th>
<th>Proportion of Patients Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis → Vitamin D, Ca++, Alendronate</td>
<td>20%-44%</td>
</tr>
<tr>
<td>Hyperlipidemia → Statin</td>
<td>75%-95%</td>
</tr>
<tr>
<td>Vitamin deficiency → Water soluble Vit A, D, E, K</td>
<td>8%-33%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastroesophageal varices associated w/ PVHTN</th>
<th>6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ EGD surveillance</td>
<td>(with early-stage disease)</td>
</tr>
<tr>
<td>▪ β-blocker</td>
<td>~31%</td>
</tr>
<tr>
<td>▪ EVBL</td>
<td>(with late-stage disease)</td>
</tr>
</tbody>
</table>

| Hepatocellular carcinoma → Surveillance imaging + AFP q 6 months | 1.5% of patients per year |

- PVHTN: Portal Venous Hypertension
- EGD: Esophagogastroduodenoscopy
- EVBL: Endoscopic Variceal Band Ligation
- AFP: Alpha-Fetoprotein
Primary Biliary Cholangitis: Hepatocellular Carcinoma

Incidence: ~1.5%/year in Cirrhotic Patients → Surveillance imaging + AFP q 6 mos

Cumulative incidence of hepatocellular carcinoma (HCC) in 99 patients with primary biliary cirrhosis (PBC) in relation to their histologic stage [stages I–III (n=60) versus stage IV (n=89)].

Deutsch et al. Eur J Gastroenterol Hepatol 2008; 20:5
Primary Biliary Cholangitis: Orthotopic Liver Transplantation (OLT)

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

Post-OLT Patient Survival

Primary Biliary Cholangitis
Recurrence of PBC After Liver Transplantation

- **PBC Recurrence:** 17-46% median of 5 yrs post-OLT
- **Diagnostic Criteria:**
  - OLT for PBC
  - AMA+
  - ↑ IgM
  - **Histology:**
    - Lymphocytic cholangitis
    - Granulomas
    - Lymphoid aggregates

Schreuder et al. Transplant Int. 2009; 22:144
Primary Sclerosing Cholangitis (PSC)
Demographics and 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%
Diagnosis of Primary Sclerosing Cholangitis: Cholestasis + Cholangiography

Vierling JM: PSC. Schiff's Liver Diseases, 12th Ed, 2017
Primary Sclerosing Cholangitis (PSC) Three Distinct Clinicopathological Entities

- Small Duct: 5-10%
- "Classic" Large Duct PSC: 90-95%
- PSC-AIH: 1-10%
- AIH: 5-10%
- Small Duct PSC
Primary Sclerosing Cholangitis (PSC) vs. Secondary Sclerosing Cholangitis

PSC

- ~75% IBD
- ~25% Non-IBD

SSC

1. IgG4 Sclerosing Cholangitis
2. Infections in Immunocompromised
   - Cryptosporidium
   - Trichosporon
   - CMV
   - Cryptococcus
   - Visceral protothecosis
   - HTLV-1-associated myelopathy
   - Sepsis/MOSF/Burns
3. Ischemic
   - Arterial injury
   - Trauma to biliary tract
4. Toxic/Ischemic
   - 5-FU intra-arterial chemotherapy
   - Formalin injection of hydatid cyst
   - Methotrexate
5. Neoplastic
   - Langerhan’s histiocytosis X
   - Systemic mastocytosis

Vierling JM: PSC. Schiff’s Liver Diseases, 12th Ed, 2017
# Primary Sclerosing Cholangitis (PSC)

Association with Multiple Autoantibodies

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

Studies (n=)

- 12 pANCA
- 6 ANA
- 3 SMA
- 3 AMA
- 1 Anti-colon
- 2 Anti-colon protein (Mr 40kDa)
- 1 Anti-endothelial cell
- 6 Miscellaneous

Primary Sclerosing Cholangitis (PSC)
Strong Disease Associations

- Celiac disease
- Rheumatoid arthritis
- Primary systemic sclerosis
- Sjögren syndrome
- Sclerosing sialoadenitis
- Rapidly progressing glomerulonephritis
- SLE
- AI hemolytic anemia
- Type 1 diabetes mellitus

Cancers

IBD
UC>>CD
“colitis”

Extra-Hepatic Autoimmune Diseases

Vierling JM: PSC. Schiff’s Liver Diseases, 12th Ed, 2017
Primary Sclerosing Cholangitis (PSC) is an independent risk factor for colorectal carcinoma.

Historic Cumulative Rate

Current Cumulative Rate


Vierling JM: PSC. Schiff’s Liver Diseases, 12th Ed, 2017
Primary Sclerosing Cholangitis (PSC) Risk Factor for Cholangiocarcinoma

Cholangiocarcinoma:
- Relative Risk = 160 to 1560
- Prevalence = 4.8% to 36.4%
- Annual incidence = 0.6% to 1.5%
- 38% to 50% of cases diagnosed within 1-year
- ~2.5% incidence in first year

Important Conclusions:
- CCA diagnosis mostly within 24 mos of diagnosis of PSC
- Long-term incidence 0.5-1.5% per year
- CCA not inevitable in PSC

Primary Sclerosing Cholangitis (PSC) Risk Factor for Gallbladder Adenocarcinoma

Gallbladder Adenocarcinoma:
- Prevalence = 0.9% to 14%
- High rate of dysplastic polyps
- Cholecystectomy appropriate:
  - Any growing polyp (regardless of size)
  - Any polyp ≥1 cm

Primary Sclerosing Cholangitis (PSC) 
Ursodeoxycholic Acid (UDCA) Therapy 

UDCA • Bile Acids

Dose?
Low (13-15 mg/kg/d: Ineffective) 
High (28-32 mg/kg/d: toxic) 
Medium (17-23 mg/kg/d: Survival benefit in a subgroup)

No! AASLD 
UDCA 
Maybe! EASL + AASLD
Long-term Survival of PSC Patients in the 5 year Scandinavian RCT of Medium Dose UDCA

Primary Sclerosing Cholangitis (PSC)
UDCA Does Not Prevent Dominant Strictures

**Occurrence of Dominant Strictures**

**Endoscopic Approaches:**
- Dilation alone?
- Dilation + Stent?
- CCA detection:
  - Cholangioscopic biopsy
  - Evaluation:
    - Dysplasia
    - FISH for aneuploidy

Primary Sclerosing Cholangitis (PSC)
Excellent Outcomes of OLT Despite Recurrence

Kaplan-Meier survival estimates

Number at risk

DBD: deceased brain-death donor
DCD: deceased cardiac donor

PSC Recurrence and Allograft Loss

Schreuder et al. Transplant Int. 2009; 22:144
Primary Sclerosing Cholangitis (PSC)
Liver Transplantation for Cholangiocarcinoma

Autoimmune Hepatitis: A Progressive Disease if Untreated

Causative factors
Immunogenetic, autoimmunity, inflammatory, PAMPs, DAMPs

Environmental Triggers

Healthy Liver

Portal Inflammation
Lymphoplasmacytic Interface Hepatitis

↑ Serum ALT/AST

At Time of Diagnosis: Often Advanced Fibrosis or Cirrhosis

Hepatocellular Necroinflammation

↑ Serum Bilirubin

Fibrosis

↓ Alb, ↓ Plat, ↑ PT INR

Cirrhosis

↑ Bilirubin

↑ Risk for HCC

Cirrhotic Liver

↑ ALT/AST; ANA, SMA, LKM1, Anti-SLA

↑ ALT/AST; ANA, SMA, LKM1, Anti-SLA
## Autoantibodies in Classification of Autoimmune Hepatitis

<table>
<thead>
<tr>
<th>AIH Type</th>
<th>AutoAbs</th>
<th>AutoAgs</th>
<th>Specificity</th>
<th>Liver</th>
<th>AIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>Histone/DNA</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMA</td>
<td>F-actin 50%</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pANCA</td>
<td>β-tubulin</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASGPR</td>
<td>ASGPR</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LKM1</td>
<td>CYP2D6</td>
<td>No</td>
<td>No (HCV infection)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LKM3</td>
<td>UGT1A</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LC-1</td>
<td>FTCD</td>
<td>Yes</td>
<td>Yes, type 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASGPR</td>
<td>ASGPR</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLA/LP</td>
<td>SepSecS protein</td>
<td>No</td>
<td>Yes (prognostic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubulin-β-5</td>
<td>ANNA</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Autoimmune Hepatitis
Extrahepatic Autoimmune and Immune-Mediated Diseases

- More common in Type 2 (40%) than Type 1 (10-20%)
- Spectrum:
  - Thyroid disease:
    - Hashimoto
    - Graves
  - Rheumatoid arthritis
  - Ulcerative colitis
  - Miscellaneous
    - Diabetes mellitus type 1
    - Sjögren syndrome
    - Vitiligo
    - Addison disease
    - Celiac sprue

## Autoimmune Hepatitis: Revised Diagnostic Criteria

**International Autoimmune Hepatitis Group**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female</th>
<th>+2</th>
<th>HLA</th>
<th>DR3 or DR4</th>
<th>+1</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP:AST (or ALT) ratio</td>
<td>&gt;3</td>
<td>-2</td>
<td>Immune disease</td>
<td>Thyroiditis, colitis, others</td>
<td>+2</td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>+2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>γ-globulin or IgG level above normal</td>
<td>&gt;2.0</td>
<td>+3</td>
<td>Other markers</td>
<td>Anti-SLA, actin, LC1, pANCA</td>
<td>+2</td>
</tr>
<tr>
<td>1.5-2.0</td>
<td>+2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0-1.5</td>
<td>+1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA, SMA, or anti-LKM1 titers</td>
<td>&gt;1:80</td>
<td>+3</td>
<td>Histological features</td>
<td>Interface hepatitis</td>
<td>+3</td>
</tr>
<tr>
<td>1:80</td>
<td>+2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:40</td>
<td>+1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1:40</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMA Positive</td>
<td>-4</td>
<td>Treatment response</td>
<td>Complete</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>Viral markers Positive</td>
<td>-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>+3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs Yes</td>
<td>-4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>+1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol &lt;25 g/day</td>
<td>+2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60 g/day</td>
<td>-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pretreatment aggregate score:**
- Definite diagnosis: >15
- Probable diagnosis: 10-5

**Post-treatment aggregate score:**
- Definite diagnosis: >17
- Probable diagnosis: 12-7

Autoimmune Hepatitis Simplified Diagnostic Criteria
International Autoimmune Hepatitis Group

Autoantibodies:
- ANA or SMA: ≥1:40 +1, ≥1:80 +2
- LKM-1: ≥1:40 +2
- Anti-SLA: Positive +2

Immunoglobulin Level
- IgG or γ-globulin: >ULN +1, >1.1 X ULN +2

Histological Features:
- Compatible with AIH +1
- Typical of AIH* +2

Absence of Viral Hepatitis:
- Yes +2
- No 0

Pretreatment Aggregate Score
- Definite Diagnosis: ≥7

Caveats:
- Whenever “Probable” or “Non-diagnostic”, recalculate score using RDC!
- SDC better for classic cases
- RDC better for complex or unusual cases
- Neither validated for use in Cholestatic Variant/Overlap Syndromes

Sahebjam F and Vierling JM Front Med, 2015
Vierling JM Clin Gastro Hepatol 2015
2010 AIH Treatment Goals
Revised the Concept of “Remission”

- Prevent progression and OLT
- Relieve symptoms
- Normalize ALT
  - <19 U/L for women
  - <30 U/L for men
- Histology:
  - Eliminate portal lymphoplasmacytic inflammation
  - Eliminate interface hepatitis
  - Prevent progression to cirrhosis
- Use combinations of immunosuppressive drugs to
  - inhibit immunopathogenetic mechanisms at multiple sites
  - minimize adverse events
Remission in Autoimmune Hepatitis
Associated with Resolution of Fibrosis, Including Cirrhosis

Presentation

Cirrhosis Resolution During Remission

After 4 years of treatment

After 12 years of treatment

Modified & Images from 2016 Tiniakos–AASLD 2016
Images from Czaja & Carpenter J Hepatology 2004

Transient Elastography

No Biochemical Remission

Biochemical Remission

LSM, Liver Stiffness Measurement in kPA units

Transient Elastography Caveats in AlH:
- Liver stiffness (LS) = fibrosis + inflammation
- ↓ LS first 6-12 mos due to ↓ inflammation
- ↓ LS thereafter indicative of ↓ fibrosis
Real world registry: 1,500 pts
41% not in remission!
(UK-AIH registry, 25% AIH pts UK)
Autoimmune Hepatitis
Conventional Immunosuppression in Responders

<table>
<thead>
<tr>
<th>Prednisone + Azathioprine</th>
<th>Budesonide</th>
<th>Prednisone Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td></td>
<td>Week 1</td>
</tr>
<tr>
<td>30 mg/d</td>
<td>3 mg TID</td>
<td>60 mg/d</td>
</tr>
<tr>
<td>Week 2</td>
<td>Azathioprine</td>
<td>Week 2</td>
</tr>
<tr>
<td>20 mg/d</td>
<td>50 mg/d or 1-2 mg/kg/d*</td>
<td>40 mg/d</td>
</tr>
<tr>
<td>Week 3</td>
<td></td>
<td>Week 3</td>
</tr>
<tr>
<td>15 mg/d</td>
<td>Azathioprine</td>
<td>30 mg/d</td>
</tr>
<tr>
<td>Week 4</td>
<td>1-2 mg/kg/d</td>
<td>Week 4</td>
</tr>
<tr>
<td>15 mg/d</td>
<td></td>
<td>30 mg/d</td>
</tr>
<tr>
<td>Maintenance:</td>
<td>10 mg/d</td>
<td>Maintenance:</td>
</tr>
<tr>
<td>10 mg/d</td>
<td>50 mg/d or 1-2 mg/kg/d</td>
<td>≤20 mg/d</td>
</tr>
</tbody>
</table>

Non-cirrhotics only!

Response

Maintenance
Taper Steroid
Continue Azathioprine

Remission
Normal ALT, γ-globulin, IgG and Histology

Slowly Withdraw Immunosuppression

Relapse

Increase Immunosuppression or Repeat Full AIH Induction Regimen

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

Eligibility Criteria for Withdrawal:
- Normal ALT/AST
- Normal IgG/γ-globulin
- No inflammation or interface hepatitis

Attempt Withdrawal of only once!

**Autoimmune Hepatitis**

**Alternative Immunosuppression for Non-Response or Partial Response**

Modified from: Vierling JM Clin Gastro Hepatol 2015

### Non-Response

- **Prednisone and/or 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

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

### Intolerance

- **Prednisone and/or Azathioprine**
  - **Week 1**: 30 mg/d (or 1-2 mg/kg/d*)
  - **Week 2**: 20 mg/d (or 1-2 mg/kg/d)
  - **Week 3**: 15 mg/d (or 1-2 mg/kg/d)
  - **Week 4**: 15 mg/d (or 1-2 mg/kg/d)
  - **Maintenance**: 10 mg/d (or 1-2 mg/kg/d)

### Partial Response

- **Verify Compliance + Optimize Dosing**

### Partial Response

- **Budesonide**
  - **Week 1**: 3 mg TID
  - **Azathioprine**
    - **Week 1**: 50 mg/d
    - **Week 2**: 50 mg/d
    - **Week 3**: 50 mg/d
    - **Week 4**: 50 mg/d (or 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

### Partial Response

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

### Non-cirrhotics only!

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

### Partial Response

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

### Non-cirrhotics only!

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

### Partial Response

- **Verify Compliance + Optimize Dosing**

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

### Partial Response

- **Verify Compliance + Optimize Dosing**

- **Empiric Use of Alternative Therapies**
  - MMF, MA, CSA, TAC, Sirolimus, Infliximab, Rituximab,
Diagnostic Criteria Based on Disease-Specific Pathogenesis Urgently Needed!

Five Postulated Explanations:

1. Distinct, independent AILDs occurring sequentially or concurrently
2. Distinct disease differing from either of the AILDs
3. Clinicopathological midpoint in a continuum of AILDs
4. One of several expressions of AIH
5. Primary AILD with ≥1 feature of another AILD (IAIHG)

Vierling JM Clin Gastro Hepatol 2015
Autoimmune Liver Diseases
Excellent Outcomes of OLT Despite Recurrence

AILDs exhibit typical and atypical features of classic AI diseases
- All associated with extrahepatic AI diseases
- PSC>>AIH associated with IBD
- PSC a premalignant disease with risk for CRC, CCA, Gallbladder adenoca

Diagnostic criteria established:
- PBC: cholestatic liver tests, AMA (+) or if AMA (-), compatible liver biopsy
- PSC: cholestatic liver tests, pANNA (68%) + MRCP or ERCP showing strictures/ectasias
  - Liver biopsy for diagnosis of small duct PSC
  - IgG4-SSC in up to 10% of previously diagnosed!
Overview PBC, PSC and AIH
Key Points 2

- AIH: revised and simplified criteria REQUIRE liver biopsy
- Fibrosis staging/monitoring with non-invasive Fibroscan
- Risk of HCC in AILDs merits surveillance imaging + AFP
- PSC: surveillance colonoscopy, MRCP?, CA-19-9?, GB imaging

Therapies:
- Established first and second line for PBC and ± AIH
  - Prognosis excellent for responders
  - Nonresponders progress
- No established therapy for PSC
  - Prognosis excellent for subgroup normalizing ALP
  - Nonresponders progress
No validated criteria for diagnosis of Overlap Syndromes
Excellent outcomes after OLT, despite recurrence in allografts
Encourage participation in clinical trials