Autoimmune Liver Disease in 2018

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Disclosures

Speaker’s Bureau: Gilead, AbbVie, Intercept
Outline

1. Autoimmune Hepatitis
2. Primary Biliary Cholangitis
3. Primary Sclerosing Cholangitis
4. IgG4 Related Sclerosing Cholangitis
Autoimmune Hepatitis
Autoimmune Hepatitis: Definition and Epidemiology

• Self perpetuating hepatocellular inflammation of unknown cause
• Characterized by the presence of:
  • Periportal hepatitis
  • Hypergammaglobulinemia
  • Serum liver-associated autoantibodies
• Exclusion of other chronic liver diseases
• Incidence - 1.9 cases per 100,000
• Frequency of AIH among patients with chronic liver disease is 11%
• Accounts for 5.9% of transplantations in the US

Manns, et al. Hepatol. 2010
Autoimmune Hepatitis: Diagnostic Approach

- Clinical Symptoms
- Biochemistry
- Autoantibodies
- Genetics
- Histopathology
- Scoring Systems
- Differential Diagnosis
Autoimmune Hepatitis: Diagnostic Approach

• Clinical Symptoms
• Biochemistry
• Autoantibodies
• Genetics
• Histopathology
• Scoring Systems
• Differential Diagnosis

Manns, et al. Hepatol. 2010
Autoimmune Hepatitis Antibodies

Liver disease of unknown origin

ANA, SMA, LMK-1, AMA

ANA+, SMA+, LKM1+, AMA+

AIH, PBC

Conventional tests negative

F-actin, SLA/LP, LC1, LKM3, PDH-E2, pANCA

Atypical pANCA+, F-actin +, SLA/LP +, LC1+ LKM3+, PDH-E2+, Negative

AIH, PSC, AIH, PBC

Cryptogenic chronic hepatitis

Manns, et al. Hepatol. 2010
Autoimmune Hepatitis Histopathology

1. Interface hepatitis or piecemeal necrosis
2. Lymphoplasmacytic infiltration
3. Hepatocyte rosettes
4. Emperiploesis (cell w/in the cytoplasm)
# Autoimmune Hepatitis Scoring System

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

- **Simplified AIH Criteria**
  - Points
    - ≤ 5 – Possible (more test)
    - 6 – Probable
    - ≥ 7 – Definite
- **Validation 11 Int’l centers**
  - Sensitivity 88%
  - Specificity 97%

<table>
<thead>
<tr>
<th>Feature/parameter</th>
<th>Discriminator</th>
<th>Score</th>
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<tbody>
<tr>
<td>ANA or SMA+</td>
<td>≥1:40</td>
<td>+1*</td>
</tr>
<tr>
<td>ANA or SMA+ or LKM+</td>
<td>≥1:80</td>
<td>+2*</td>
</tr>
<tr>
<td>or SLA/LP+</td>
<td>Any titer</td>
<td>+2*</td>
</tr>
<tr>
<td>IgG or γ-globulins level</td>
<td>&gt;upper limit of normal</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>&gt;1.1x upper limit</td>
<td>+2</td>
</tr>
<tr>
<td>Liver histology (evidence of hepatitis is a necessary condition)</td>
<td>Compatible with AIH</td>
<td>+1</td>
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<tr>
<td></td>
<td>Typical of AIH</td>
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<tr>
<td></td>
<td>Atypical</td>
<td>0</td>
</tr>
<tr>
<td>Absence of viral hepatitis</td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>+2</td>
</tr>
</tbody>
</table>

Autoimmune Hepatitis Treatment

Indications

1. Aminotransferases 10 x ULN
2. Gamma Globulins 2 x ULN
3. Aminotransferases 2 x ULN
   a. Symptoms
   b. Elevated gamma globulins
   c. Direct hyperbilirubinemia
   d. Biopsy with interface hepatitis
4. Cirrhosis with histological proof of inflammation
5. Children
# Autoimmune Hepatitis Initial Treatment

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Combination Therapy</th>
<th>Azathioprine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone (mg/day)</td>
<td>Prednisone (mg/day)</td>
<td>USA (mg/day)</td>
</tr>
<tr>
<td>Week 1</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>Week 2</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>Week 3</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Week 4</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Maintenance-Therapy</td>
<td>20 and less</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons for Choice of Therapy</th>
<th>Cytopenia</th>
<th>Postmenopausal</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Thiopeurinmethyltransferase-Deficiency</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
<td>uncontrolled Diabetes, Hypertension,</td>
</tr>
<tr>
<td></td>
<td>Tumors</td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Therapy ≤6 Mo</td>
<td>Acne</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emotional Instability</td>
</tr>
</tbody>
</table>

EU (mg/kg/day) 1-2
Definition of Response in Autoimmune Hepatitis

• Remission: 65 – 80% → symptom resolution, NL ALT/AST/Bili

• Incomplete Response: ~13% → Some improvement in clinical, lab and histology despite compliance for 2 years

• Treatment Failure: ~10-15% → persistent biochemical and histological activity with development of cirrhosis / LT
  - Cirrhosis
  - Younger / children
  - Specific HLA
Autoimmune Hepatitis Second Line Therapy

**Budesonide**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Complete response at 6 months</th>
<th>Complete response at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>100 103</td>
<td>88 85</td>
</tr>
<tr>
<td>PP</td>
<td>76 82</td>
<td>173</td>
</tr>
</tbody>
</table>

**A. Gender**
- Male: 30 15
- Female: 70 88

**B. Body weight**
- ≤ 60kg: 20 19
- > 60kg: 60 55

**C. HLA DR3/DR4**
- HLA DR3+: 28 44
- HLA DR4+: 24 22

<table>
<thead>
<tr>
<th>Responers</th>
<th>Complete biochemical remission at 6 months (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>21 3</td>
</tr>
<tr>
<td>Female</td>
<td>39 37</td>
</tr>
</tbody>
</table>

Role of Budesonide in Autoimmune Hepatitis

• Reduce steroid related side effects
  • Induction of remission and maintenance
• Avoid in cirrhotics
  • Portal hypertension and loss of topical effects
• Long term risk and benefits
  • Unknown
• Limited benefit in prednisone dependent or unresponsive
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

**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

**Budesonide**

- **3 mg TID** +
- **Azathioprine**

- **1–2 mg/kg/d**

**Response**

- Maintenance
- Taper steroid
- Continue azathioprine

**Remission**

- Normal ALT, γ-globulin, IgG, and histology

**Withdraw immunosuppression**

- Remission maintained
- Monitor for relapse

**Intolerance**

- Prednisone and/or azathioprine

**Repeat induction regimen**

**Relapse**

- Empirc use of alternative therapies
  - MMF, MA, CSA, TAC, rituximab, sirolimus, everolimus, infliximab

**Non-response**

- Verify compliance
- Optimize dosing

**Fail to achieve remission**

- Fail to achieve remission
Autoimmune Hepatitis Second Line Therapy

**Mycophenolate Mofetil**

- Blocks de novo purine synthesis
- Recommended in patients refractory to conventional therapy or intolerant to azathioprine
- Significant improvement in biochemical response
- 30% discontinuation due to side effects
- ~ 60% remission and 35% prednisone withdrawal.
- Effect was sustained

Primary Biliary Cholangitis
Primary Biliary Cholangitis

• Slowly progressive autoimmune liver disease

• 90% females

• Peak incidence in 40’s (30-60’s)

• Lymphocytic portal inflammation and autoimmune destruction of intrahepatic bile ducts

• 90-95% + AMA

• Leads to cirrhosis and liver failure
  • Main indication of LT in 80s

Kumagi T, et al. Orphanet J Rare Dis. 2008
Primary Biliary Cholangitis: Pathophysiology

• Environmental triggers

• Susceptible host

• Genetic predisposition
  • Humoral and cellular response to intracytoplasmic antigen
  • Highly specific autoantibodies
  • T lymphocyte mediated bile duct destruction
Primary Biliary Cholangitis: Symptoms and Diseases

• Symptoms
  • ~50% asymptomatic at diagnosis
  • Fatigue and pruritus most common symptoms~20%

• Associated conditions
  • Autoimmune diseases: Sjogren's, CREST, Raynaud's, Thyroiditis
  • Hypercholesterolemia
  • Celiac Disease
  • Metabolic Bone disease

• Complications
  • Portal hypertension
  • liver failure
  • HCC

Primary Biliary Cholangitis: Diagnosis

3 Diagnostic criteria

1. Cholestatic liver injury
   - ALP > 1.5x ULN
   - AST < 5x ULN

2. + AMA (> 1:40)

3. Histopathology

Histolopathology

Stage I – Florid duct lesion
Stage II – Interface hepatitis and ductular proliferation
Stage III – Bridging Fibrosis
Stage IV – Cirrhosis
3 Diagnostic criteria

1. Cholestatic liver injury
   - ALP > 1.5x ULN
   - AST < 5x ULN

2. + AMA

3. Histopathology
   - Stage I – Florid duct lesion
   - Stage II – Interface hepatitis and ductular proliferation
   - Stage III – Bridging Fibrosis
   - Stage IV – Cirrhosis

Bile duct
Inflammation
UDCA for Primary Biliary Cholangitis

- UDCA 13-15 mg/Kg
- Mechanism
  - Modulates HLA expression
  - Stabilizes canalicular membrane
  - Choleretic
- Outcomes
  - Improves survival
  - Improves fibrosis
  - Improves transplant free survival
  - Decreases rates of HCC


Primary Biliary Cholangitis: Treatment Response

• Independent predictors of LT/death
  ▪ Bilirubin > 1 mg/dL
  ▪ ≥ Stage 3 Fibrosis
  ▪ Interface hepatitis
  ▪ Absence of biochemical response

Assessing Response and Prognosis in PBC

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical + APRI(^1) (2014)</td>
<td>Biochemical response (Barcelona, Paris-I/II, or Toronto) and APRI ≤0.54 after 1 year UDCA</td>
</tr>
<tr>
<td>UK-PBC Risk Score(^2) (2015)</td>
<td>Prognostic index comprising baseline albumin and platelet count, plus bilirubin, ALT or AST, and ALP after 1 year UDCA</td>
</tr>
<tr>
<td>GLOBE Score(^3) (2015)</td>
<td>Prognostic index comprising baseline age, and bilirubin, ALP, albumin, and platelet count after 1 year UDCA</td>
</tr>
</tbody>
</table>
Obeticholic Acid for Primary Biliary Cholangitis

• Obeticholic Acid
  • Derivatie of chenodeoxycholic acid
  • Selective FXR (Farnesoid X Receptor) agonist
  • Mechanism of action
    • Regulates bile acid synthesis, transport and intrahepatic bile flow
    • Antiinflammatory properties (Decreasing NF-KB, IL-1, IL-6, IL-12)
    • Antifibrotic (Regulates stellate cell activation apoptosis)
OCA for Primary Biliary Cholangitis

Primary Endpoints
1. ALP < 1.67x ULN
2. Normal bilirubin
3. ≥ 15% reduction in ALP

Primary Endpoints at 12 months
- Titration group (46%)
- 10 mg group (47%)
- Placebo group (10%)
- P < 0.001 for both comparisons

Primary Sclerosing Cholangitis
Primary Sclerosing Cholangitis

• A chronic inflammatory cholestatic disease
• Progressive destruction of bile ducts
• May progress to cirrhosis
• Etiology unknown
• Autoantibodies:
  • 95% patients with PSC have at least one autoantibody
  • 85% +ve ANCA
  • 50% +ve ANA
  • 25% +ve SMA
Primary Sclerosing Cholangitis

• Usually diagnosed in 20s and 30s
• Male predominance ~3:1
• 80% have IBD – usually UC
• ~44% asymptomatic at diagnosis
• Median survival ~ 12 years

• Cholangiocarcinoma
  • Lifetime prevalence of 10-30%
  • Annual risk 1.5% per year
  • Difficult to diagnose
  • Patients also have late risk of HCC
Primary Sclerosing Cholangitis Diagnosis

MRCP

ERCP

Biopsy
Primary Sclerosing Cholangitis Treatment

Recommendations:

28. In adult patients with PSC, we recommend against the use of UDCA as medical therapy (1A).

Recommendations

1. The available data base shows that UDCA (15–20 mg/d) improves serum liver tests and surrogate markers of prognosis (I/B1), but does not reveal a proven benefit on survival (III/C2). The limited data base does not yet allow a specific recommendation for the general use of UDCA in PSC.

Recommendation

1. Ursodeoxycholic acid (UDCA) in doses >28 mg/kg/day should not be used for the management of patients with PSC. (Strong recommendation and high quality of evidence) (42)
PSC: Survival of PSC Events According to Baseline ALP

N at Risk Events
- ALP (U/L) < 158
- ALP (U/L) 158 - < 325
- ALP (U/L) ≥ 325

Levy C, et al. 2017
UDCA for Primary Sclerosing Cholangitis

UDCA for Primary Sclerosing Cholangitis

A

B

C

D

E

Wunsch E, et al. Hepatol 2014
UDCA for Primary Sclerosing Cholangitis

• Low dose → 13 – 15 mg/Kg/d
  1. Improves biochemistries
  2. No change in survival

• Medium dose → 17 – 23 mg/Kg/d
  1. Improves biochemistries
  2. Trend to improved survival

• High dose → 28 – 30 mg/Kg/d
  1. Improves biochemistries
  2. Increased rates of death / decompensation / LT
IgG4 Related Sclerosing Cholangitis
IgG4 Related Sclerosing Cholangitis

• Distinct from PSC
• Most frequent manifestation of IgG4 Autoimmune Pancreatitis
• Male predominance (8:1)
• Differential KEY: PSC v. IgG4SC v Cholangio Ca

• Presentation
  • Multiple organs
  • Single stricture

• Diagnostic criteria are lacking
  • +IgG4 plasma cell infiltrate in biopsies
  • Interstitial fibrosis
  • Elevated IgG4 levels (>135 mg/dL)
  • Steroid responsiveness

## Summary

<table>
<thead>
<tr>
<th>Disease</th>
<th>AIH</th>
<th>PBC</th>
<th>PSC</th>
<th>IgG4 SC</th>
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<tbody>
<tr>
<td>Location</td>
<td>Hepatocytes</td>
<td>Intrahepatic BD</td>
<td>Extrahepatic BD</td>
<td>Extrahepatic BD</td>
</tr>
<tr>
<td>Markers</td>
<td>ANA, ASMA, LKM</td>
<td>AMA</td>
<td>P-ANCA</td>
<td>ANA, IgG4 level</td>
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<tr>
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<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
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<tr>
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<td>Any</td>
<td>40’s</td>
<td>40’s</td>
<td>60-70’s</td>
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<td>Serology and Biopsy</td>
<td>Serology</td>
<td>Imaging</td>
<td>Serology and Biopsy</td>
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<td>Immunosuppression</td>
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<td>Immunosuppression</td>
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