Autoimmune Hepatitis and Overlap Syndrome

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Autoimmune Hepatitis
Demographics and Epidemiology

- Uncommon
- Afflicts ~200,000 in U.S.A.
- Incidence 1.9 per $10^5$ per year
- Prevalence 16.9 per $10^5$
- Female to male ratio= 4:1
- Afflicts both children and adults
- Bimodal age distribution: 10-20 vs. 45-75 yrs
- 6% liver transplants in US
- 40% mortality in symptomatic patients
  ≤6 months if untreated
Autoimmune Hepatitis
Clinical Spectrum

Acute Hepatitis
- 25-30%
- Usually younger
- Icteric acute viral hepatitis-like picture

Asymptomatic
- 15-20%
- Extrahepatic manifestations may be present

Fulminant Hepatic Failure
- ~5%
- Potentially reversible without OLT

Symptomatic Chronic Hepatitis
- 50%
- Fatigue, malaise
- Physical findings:
  - Hepatomegaly (78%)
  - Splenomegaly (32-56%)
  - Jaundice (46%)

Cryptogenic Cirrhosis:
- < 5%
- Decompensated PVHTN event
AIH
Clinical Presentations

Extrahepatic Autoimmune Manifestations
- AIH Type 2 (40%) > AIH Type 1 (10%)
- Spectrum
  - Thyroid disease (Hashimoto’s, Graves)
  - Rheumatoid arthritis
  - Miscellaneous
    - Diabetes mellitus type 1
    - Sjogren’s syndrome
    - Vitiligo
    - Addison’s
    - Celiac sprue

AIH
Laboratory Testing

Anticipated Results:
- Elevated aminotransferases
  - Usually not more than 500 U/L
  - \( \text{ALT} \geq \text{AST} \)
- \( \pm \) Elevated bilirubin
- Moderately elevated alkaline phosphatase
- Immunoglobulins
  - SPE \( \rightarrow \) Hypergammaglobulinemia
  - Immunelectrophoresis \( \rightarrow \) Elevated IgG
AIH
Diagnostic Strategy

Exclude other causes of liver disease!
- Viral hepatitis C
- Alpha-1 antitrypsin deficiency
- Cholestatic autoimmune diseases
  - PBC
  - PSC
- Wilson’s Disease
- Alcohol
- Drug hepatotoxicity
  - Minocycline
  - Anti-epileptics

AIH
Sequential Autoantibody Testing

[Diagram showing the sequence of autoantibody testing and positive/negative outcomes]

Table 2: Diagnostic Scoring System for Atypical Autoimmune Hepatitis in Adults

<table>
<thead>
<tr>
<th>Category</th>
<th>Factor</th>
<th>Score</th>
<th>Category</th>
<th>Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
<td>+2</td>
<td>Concurrent immune disease</td>
<td>Any nonhepatic disease of an immune nature</td>
<td>+2</td>
</tr>
<tr>
<td>AST/ALT (or ALT ratio)</td>
<td>&gt;3</td>
<td>-2</td>
<td>Other autoantibodies*</td>
<td>Anti-SLA/IC, acte, LG2, pANCA</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 (times above upper limit of normal)</td>
<td>&gt;2.0</td>
<td>+3</td>
<td>Histologic features</td>
<td>Interface hepatitis</td>
<td>+3</td>
</tr>
<tr>
<td>1.5-2.0</td>
<td>+2</td>
<td>Plasma cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0-1.5</td>
<td>+1</td>
<td></td>
<td>Rousettes</td>
<td></td>
<td>+1</td>
</tr>
<tr>
<td>&lt;1.0</td>
<td>0</td>
<td>None of above</td>
<td></td>
<td></td>
<td>-5</td>
</tr>
<tr>
<td>ANA, SMA, or anti-LKM1 titers</td>
<td>&gt;1:80</td>
<td>+3</td>
<td>HLA</td>
<td>DR3 or DR4</td>
<td>+1</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>ANA</td>
<td>Positive</td>
<td>-4</td>
<td>Treatment response</td>
<td>Remission alone</td>
<td>+2</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>+3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral markers of active infection</td>
<td>Positive</td>
<td>-3</td>
<td>Pretest score</td>
<td>&gt;15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>+3</td>
<td>Definite diagnosis</td>
<td>10-15</td>
<td></td>
</tr>
<tr>
<td>Hepatotoxic drugs</td>
<td>Yes</td>
<td>-4</td>
<td>Probable diagnosis</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</td>
<td>&lt;25 g/d</td>
<td>+2</td>
<td>Posttest score</td>
<td>&gt;17</td>
<td></td>
</tr>
<tr>
<td>&gt;60 g/d</td>
<td>-2</td>
<td>Definite diagnosis</td>
<td></td>
<td>12-17</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Probable diagnosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Fatigue, jaundice, nausea, abdominal pain, female gender

Elevated AST/ALT (> ALKP)

Drug history: minocycline, diclofenac, propylthiouracil, nitrofurantoin, methyldopa, isoniazid

Negative viral hepatitis serologies

ANA, SMA, anti-LKM1 > 1:80
IgG > 1.5x ULN

AMA negative

Normal serum copper, α<sub>2</sub> antitrypsin, ceruloplasmin

Histology: interface hepatitis, plasma cell infiltration

Diagnosis of autoimmune hepatitis
<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone alone</td>
<td>40mg - 60mg PO daily</td>
</tr>
<tr>
<td></td>
<td>Taper down to 10mg daily in 4 weeks</td>
</tr>
<tr>
<td></td>
<td>(depending on treatment response)</td>
</tr>
<tr>
<td><strong>Preferred Regimen</strong></td>
<td></td>
</tr>
<tr>
<td>Prednisone + Azathioprine*</td>
<td>30mg PO daily + 50mg PO daily</td>
</tr>
<tr>
<td>Budesonide + Azathioprine*</td>
<td>3mg PO TID + 50mg PO daily</td>
</tr>
</tbody>
</table>

*Azathioprine: Monitor for leukopenia, thrombocytopenia; Azathioprine: Pregnancy category D
Autoimmune Hepatitis

Benefits of Prednisolone Therapy


Probabilities of Survival During Steroid Therapy

Czaja A, 2003
85% who enter remission do so within 2 years.
## AIH Treatment

### Old and New Approaches to Immunosuppression

<table>
<thead>
<tr>
<th>Agents</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid</td>
<td>Positive randomized, controlled trials</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Positive, open label trials</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Positive, open label trials</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Positive, open label trials</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Positive, open label trials</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Investigational</td>
</tr>
<tr>
<td>rHuIL-10</td>
<td>Investigational</td>
</tr>
</tbody>
</table>


---

## TREATMENT END POINTS

<table>
<thead>
<tr>
<th>End Point</th>
<th>Definition</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>AST&lt; 2X ULN&lt;br&gt;Histology inactive or portal hepatitis</td>
<td>Taper prednisone&lt;br&gt;azathioprine&lt;br&gt;Monitor liver tests</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td>AST/TB with elevation (66% of pretreatment level), clinical deterioration</td>
<td>Higher prednisone/azathioprine doses or other regimen</td>
</tr>
<tr>
<td>Intolerance to Therapy</td>
<td>Obesity, depression, diabetes, osteoporosis, cytopenia, cholestasis</td>
<td>Dose reduction, 6-MP, other regimen</td>
</tr>
</tbody>
</table>
TREATMENT END POINTS

- Liver biopsy best method to determine clinical remission
  - Should be considered before termination of therapy
  - Normal hepatic architecture associated with a 20% relapse rate after drug withdrawal
  - Portal hepatitis associated with a 50% frequency of relapse
  - Progression to cirrhosis or persistence of interface hepatitis is associated with an 86% to 100% frequency of relapse
- Histological improvement lags behind clinical and laboratory improvement by 3 to 6 months

AIH
Response to Therapy

- Remission
- Incomplete Response
- Non-Response
- AST > 2 X ULN Symptoms
- ↑ AST
- ↑ Bilirubin
- Histological worsening
- Ascites, PSE

Alternative Rx
- Mycophenolate
- Cyclosporine
- Tacrolimus
- Ursodiol

End of Therapy Liver Histology Predicts Relapse

Normal Histology
Interface Hepatitis
Inactive Cirrhosis
Portal Plasma Cells

Risk of Relapse (%)

0 20 40 60


Autoimmune Hepatitis

Maintenance Therapy

- Lowest effective dose for Prednisone $\leq 10$ mg/d
  or
- Azathioprine, 1.5-2.0 mg/kg/d
  or
- Low dose Prednisone $\leq 10$mg/d plus Azathioprine 50 mg/d
  - Add Vitamin D (50,000 U/wk) and Ca (1-1.5 g/d) to Prednisone
  - Monitor for hypertension, cataracts, glaucoma, bone disease in Prednisone recipients
  - Monitor WBC, platelets in Azathioprine recipients
### Course After Orthotopic Liver Transplantation

<table>
<thead>
<tr>
<th>Post-OLT Follow-Up (Months)</th>
<th>Survival</th>
<th>SMA</th>
<th>ANA</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>0</td>
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<tr>
<td>12</td>
<td>80</td>
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<td>0</td>
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<tr>
<td>18</td>
<td>70</td>
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<td>24</td>
<td>60</td>
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<td>30</td>
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<td>36</td>
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<tr>
<td>42</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>48</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Update on Autoimmune Liver Diseases

#### Summary

<table>
<thead>
<tr>
<th>Feature</th>
<th>PBC</th>
<th>PSC</th>
<th>AIH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>$400/10^6$</td>
<td>$40/10^6$</td>
<td>$17/10^5$</td>
</tr>
<tr>
<td>Gender predominance</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>Adults</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Familial</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Associated diseases</td>
<td>AI diseases</td>
<td>IBD</td>
<td>AI Diseases</td>
</tr>
<tr>
<td>Infectious etiology?</td>
<td>Possibly</td>
<td>Unlikely</td>
<td>Possibly</td>
</tr>
<tr>
<td>Disease-specific AutoAbs</td>
<td>AMA, ANAs</td>
<td>None</td>
<td>SLA/LP</td>
</tr>
<tr>
<td>Validated prognostic models</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Complications</td>
<td>HCC</td>
<td>AdenoCa</td>
<td>HCC</td>
</tr>
<tr>
<td>UDCA safe and effective</td>
<td>Yes</td>
<td>Yes*</td>
<td>No</td>
</tr>
<tr>
<td>Immunosuppression effective</td>
<td>Early stages</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>OLT effective but with recurrence</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*20-30 mg/kg/d
Autoimmune Hepatitis Overlap Syndromes
Differential Diagnostic Dilemmas

Variants of Autoimmune Hepatitis

- AMA positive without features of PBC
- Bile duct lesions in otherwise overt AIH
- Acute AIH plus viral hepatitis
- Cryptogenic AIH (no autoantibodies)
- Cholestatic AIH with co-existent PSC
Medical Challenges: Diagnosis

- 2-19% PBC
- 7-14% PSC
- Believed to have overlap with clinical, biochemical, serological, histological criteria
- Sequential development may occur
- Clinical significance is in the treatment options!

IAIHG Position Statement 2011

Autoimmune Hepatitis

Prevalence of ANA in Liver Disease

![Bar chart showing prevalence of ANA in different liver diseases]
Overlap Syndromes

<table>
<thead>
<tr>
<th>Diagnostic Criteria</th>
<th>AIH</th>
<th>PBC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>malaise, jaundice</td>
<td>fatigue, pruritus</td>
<td>fatigue pruritus</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>occasionally</td>
<td>often</td>
<td>often</td>
</tr>
<tr>
<td>Gender</td>
<td>female&gt;male</td>
<td>female&gt;male</td>
<td>female&gt;male</td>
</tr>
<tr>
<td>Biochemistry</td>
<td>↑ALT</td>
<td>↑ALP</td>
<td>↑ALP and/or GGT</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>↑IgG</td>
<td>↑IgM</td>
<td>± IgM/IgG</td>
</tr>
<tr>
<td>(low Ig A type2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>SMA/anti LKM1</td>
<td>AMA</td>
<td>none specific</td>
</tr>
<tr>
<td>ERC/MRC</td>
<td>overlap PSC (young)</td>
<td>normal</td>
<td>Diagnostic hallmark</td>
</tr>
</tbody>
</table>

PSC Diagnosed

ALT 5X ULN
IgG 2X ULN

Disproportionally elevated serum transaminases and/or IgG levels

Predominance of cholestatic findings

Consider a liver biopsy for assessment of histological features of AIH (interface hepatitis)

Treatment should be individualized and adjusted according to the response, with careful attention to side effects

Consider treatment with corticosteroids ± other immunosuppressive agents***, with or without UDCA****

IAIHG Position Statement 2011
Overlap: serologies not that helpful

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-neutrophil cytoplasmic antibody</td>
<td>50%-80%</td>
</tr>
<tr>
<td>Anti-nuclear antibody</td>
<td>7%-77%</td>
</tr>
<tr>
<td>Anti-smooth muscle antibody</td>
<td>13%-20%</td>
</tr>
<tr>
<td>Anti-endothelial cell antibody</td>
<td>35%</td>
</tr>
<tr>
<td>Anti-cardiolipin antibody</td>
<td>4%-66%</td>
</tr>
<tr>
<td>Thyroperoxidase</td>
<td>7%-16%</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>4%</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>15%</td>
</tr>
</tbody>
</table>

Medical Challenges: Overlap

- **Treatment**
  - AIH: Standard treatment
    - Prednisone + AZA
    - Responsive less often
    - Progression to transplant more common

Medical Challenge: IAC

- Immunoglobulin Associated Cholangiopathy
  - Cholangiographically looks like PSC
  - Distinct histology
  - 127 pts Mayo clinic dx’d with PSC
    - 7% had elevated IgG4
      - Worse tests, higher Mayo risk score
      - Shorter time to transplant and aggressive course pre/post OLT
  - Treatment response to steroids!
    - 40% re to steroids in 11 weeks
    - Resolution of strictures


<table>
<thead>
<tr>
<th>PATHOLOGY</th>
<th>DEFINITIVE IAC FEATURES:</th>
<th>PROBABLE IAC</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile duct has LPC infiltrate with &gt; 10 IgG4 positive cells per hpf.</td>
<td>pancreatic/biliary resection or core pancreatic biopsy with supporting pathology. OR Classic radiographic features of AIP plus elevated serum IgG4 (&gt;140 mg/dL).</td>
<td>2 or more of the following:  • elevated serum IgG4  • Other organ involvement (ex. retroperitoneal fibrosis).  • Supporting bile duct biopsy.  • Suggestive pancreatic imaging</td>
<td>Coexisting IBD is uncommon.</td>
</tr>
</tbody>
</table>

Management: For definitive IAC, corticosteroids for 11 weeks and consideration of azathioprine for maintenance of remission. For probable IAC, corticosteroids for 4 weeks, if responsive then continue to treat as definitive IAC.
Serum IgG4 levels > 2xULN

- PSC patients with serum IgG4 > 2 X ULN
- Endpoints: mortality, portal HTN, CCA, CR
- 349 pts: 14% with abnormal IgG4
  median f/u 5 years

Higher frequency of Cholangiocarcinoma

7/24 (29%) vs. 42/325 (12.9%)

p = 0.03


Primary Biliary **Cholangitis**: Background

- First described in 1857, but not well characterized until 1970’s
- Chronic, slowly progressive liver disease
- Autoimmune in origin
- Anti-mitochondrial antibody is key in diagnosis
Clinical Presentation

• Asymptomatic
  – 20-80% can have no symptoms
  – Duration of no symptoms variable 6-10 years
  – Present with elevated alkaline phosphatase or +AMA
  – Osteoporosis or other extrahepatic associations with PBC

PBC

• Differential diagnosis: extra-hepatic biliary obstruction, primary sclerosing cholangitis, drug-induced cholestasis, sarcoidosis, hepatitis C and overlap with autoimmune hepatitis

• Complications of PBC include pruritus, osteopenia, fat soluble vitamin deficiency and hypercholesterolemia
Overlap Syndromes

French Scoring System for PBC and AIH Overlap

AIH defined by two or more:

- ALT > 5x normal
- SMA positive and/or Ig G > 2 normal
- Liver biopsy with piecemeal necrosis (moderate/severe)

Chazouillères, Hepatology 1998; 28:296

Associations with PBC

<table>
<thead>
<tr>
<th>Osteoporosis</th>
<th>Sicca syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthropathy/arthritis</td>
<td>Skin disorders</td>
</tr>
<tr>
<td>Sjogren’s syndrome</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>Raynaud’s disease</td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Gallstones</td>
</tr>
<tr>
<td>CREST syndrome</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>SLE</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>Hashimoto thyroiditis</td>
</tr>
</tbody>
</table>
Clinical Presentation

• Symptomatic
  – Pruritus, scratch marks
  – Fatigue (most common)
  – Abdominal pain
  – Hepato/splenomegaly
  – Jaundice
• No strong evidence that having symptoms or not predicts histologic stage

Pruritus

• Very common (20-60%)
• Usually precedes jaundice
• May occur first in pregnancy
• Begins in perianal/genital region or on surfaces of palm/soles
• Worse in evening, winter, with dry skin
• NOT effectively eased by scratching
Diagnosis

- Elevated liver enzymes
  - Alkaline phosphatase
- Positive AMA
- Diagnostic liver biopsy findings
- Two or more is “probable” diagnosis
  - 80% go on to develop classic picture

PRIMARY BILIARY CIRRHOSIS
Autoantibodies

<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>Sp100</td>
<td>21</td>
</tr>
<tr>
<td>Promyelocytic leukemia protein</td>
<td>19</td>
</tr>
<tr>
<td>gp210</td>
<td>26</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>
<tr>
<td>Bile canaliculi</td>
<td>35</td>
</tr>
<tr>
<td>Endomyisium</td>
<td>11</td>
</tr>
<tr>
<td>Hsp65kD</td>
<td>100</td>
</tr>
<tr>
<td>Platelet (GP Ib/IX, GP Ib/IIa)</td>
<td>39</td>
</tr>
<tr>
<td>Alpha-enolase</td>
<td>29</td>
</tr>
<tr>
<td>Lipid A</td>
<td>100</td>
</tr>
</tbody>
</table>
AMA

- How good is the test?
  - 98% sensitive
  - 96% specific
- 10-15% PBC are AMA-negative
- May be detectable years before any other abnormalities
- Titers DO NOT correlate to disease severity
  - AMA may decrease after liver tx
### Alkaline phosphatase

- Classic cholestatic enzyme
- Reaches plateau early in disease
- Slightly abnormal $\rightarrow$ 1500-2000 U/l
- More elevated than AST/ALT
- Fluctuates by 20-30%
- Not related to rate of progression

### Bilirubin

- Rises in all patients at end stage of disease
- Best prognostic indicator
- Bilirubin $>$6: life expectancy 25 months
  $>$10: life expectancy 20 months
Treatment

• No specific treatment has definitively improved survival benefit
• Three agents: ursodiol, azathiaprine, and cyclosporine have the strongest scientific proof of efficacy
• Based on current evidence, ursodiol is safest and potentially most effect

Treatment: Urso

• 11 placebo controlled randomized trials
• Associated with diminution of symptoms, improvement in biochemical tests, variable effect on histology
• Trend towards delay in liver transplant in 2 studies
Overlap Syndromes

- Diagnosis made when a single designation is inadequate to convey the mix of clinical, laboratory, and histologic features of a disease process
  - AIH but with AMA, high alkaline phosphatase, biliary pathology
  - PBC but with markedly elevated transaminases, elevated IgG, interface hepatitis

Response to combination therapy

![Graphs showing biochemical changes in patients treated by UDCA alone (UDCA) and in patients treated by combined therapy (UDCA + BS). Data given as box plots representing 10, 25, 50 (— median), 75 and 90 percentiles. * P<0.05, ** P<0.01 vs start values.](image-url)
Comparison of Response to UDCA Therapy in Classical PBC With or Without Features of AIH

Joshi et al., Hepatology 2002;35:411

Diagnostic features of the overlap syndromes of autoimmune hepatitis (AIH)

<table>
<thead>
<tr>
<th>Overlap syndrome</th>
<th>Laboratory features</th>
<th>Serological features</th>
<th>Histological features</th>
<th>Cholangiographic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIH-PBC</td>
<td>Consistent with Paris criteria* (19,30)</td>
<td>AMA positive (2)</td>
<td>Interface hepatitis (30)</td>
<td>Normal (6)</td>
</tr>
<tr>
<td></td>
<td>Mild forms may have AP &lt;2xULN (2,6)</td>
<td></td>
<td>Destructive cholangitis (fond duct lesions) (30)</td>
<td></td>
</tr>
<tr>
<td>AIH-PSC</td>
<td>AST/ALT&gt;ULN (2)</td>
<td>AMA negative (2)</td>
<td>Interface hepatitis (34)</td>
<td>Bile duct strictures (2,18,20,72)</td>
</tr>
<tr>
<td></td>
<td>y-globulin and IgG &gt;ULN (2)</td>
<td></td>
<td>Ductopenia (34)</td>
<td></td>
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<tr>
<td></td>
<td>AP or GGT&gt;ULN (2)</td>
<td></td>
<td>Portal edema or fibrous (34)</td>
<td></td>
</tr>
<tr>
<td>AIH-cholestatic</td>
<td>AST/ALT&gt;ULN (2)</td>
<td>AMA negative (2)</td>
<td>Obliterative fibrous cholangitis (rare) (34)</td>
<td>Normal (2,11,27)</td>
</tr>
<tr>
<td>syndrome</td>
<td>y-globulin and IgG &gt;ULN (2)</td>
<td></td>
<td>Interface hepatitis (34)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AP or GGT &gt;ULN (2)</td>
<td></td>
<td>Destructive cholangitis or bile duct loss (11,27)</td>
<td></td>
</tr>
</tbody>
</table>
Summary

• Diagnosis of AIH and overlap syndromes can be challenging
  – Awareness
  – Biopsy findings
  – Look for dominant process
• Combination therapy beneficial