Autoimmune Hepatitis: When First Line Therapy Does Not Work

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Autoimmune Hepatitis (AIH)

Definition:

- Syndrome of progressive hepatitis characterized by loss of tolerance to hepatic autoantigens that results in:
  - Hepatocellular necroinflammation
  - Autoantibodies: non-organ, non-species-specific
  - Hypergammaglobulinemia and/or IgG
  - Non-pathognomonic histopathology
  - Responsiveness to immunosuppressive medications
Autoimmune Hepatitis Classification Based on Autoantibodies

<table>
<thead>
<tr>
<th>Types</th>
<th>1 (95-97%)</th>
<th>2 (3-5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AutoAbs</td>
<td>ANA &amp;/or SMA (f-actin ELISA)</td>
<td>LKM1</td>
</tr>
<tr>
<td></td>
<td>SLA/LP pANCA</td>
<td>SLA/LP</td>
</tr>
<tr>
<td></td>
<td>LC-1 ASGPR</td>
<td>LKM3</td>
</tr>
</tbody>
</table>
Autoimmune Hepatitis: Diagnosis Requires a Liver Biopsy

Characteristic Feature Interface Hepatitis

= Interface Hepatitis
# Autoimmune Hepatitis

Revised Scoring System of the 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></td>
<td>&lt;1.5</td>
<td>+2</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></td>
<td>1.5-2.0</td>
<td>+2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0-1.5</td>
<td>+1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;1.0</td>
<td>0</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></td>
<td>1:80</td>
<td>+2</td>
<td></td>
<td>Plasmacytic</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>1:40</td>
<td>+1</td>
<td></td>
<td>Rosettes</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>&lt;1:40</td>
<td>0</td>
<td></td>
<td>None of above</td>
<td>-5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Biliary changes</td>
<td>-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other features</td>
<td>-3</td>
</tr>
<tr>
<td>AMA</td>
<td>Positive</td>
<td>-4</td>
<td>Treatment response</td>
<td>Complete</td>
<td>+2</td>
</tr>
<tr>
<td>Viral markers</td>
<td>Positive</td>
<td>-3</td>
<td></td>
<td>Relapse</td>
<td>+3</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>+3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Yes</td>
<td>-4</td>
<td>Pretreatment aggregate score:</td>
<td>Definite diagnosis</td>
<td>&gt;15</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>+1</td>
<td>Probable diagnosis</td>
<td>10-15</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>&lt;25 g/day</td>
<td>+2</td>
<td>Post-treatment aggregate score:</td>
<td>Definite diagnosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;60 g/day</td>
<td>-2</td>
<td></td>
<td>&gt;17</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Probable diagnosis</td>
<td>12-17</td>
<td></td>
</tr>
</tbody>
</table>

# Differential Diagnostic Dilemmas

## Autoantibodies Observed in Other Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>ANA/SMA</th>
<th>LKM1</th>
<th>LKM2</th>
<th>LKM3</th>
<th>SLA/LP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Hepatitis</td>
<td>80% +</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Chronic HCV</td>
<td>20-25%+</td>
<td>0-88%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HBV-HDV</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>13%</td>
<td>–</td>
</tr>
<tr>
<td>Alcoholic Hepatitis</td>
<td>75%+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Wilson Disease</td>
<td>Common*</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Acute phase reaction normalizes ceruloplasmin concentration!!

Test [Cu]: 24 hour urine (>100 g) & hepatic (250 g/g dry wt)
Autoimmune Hepatitis Requires a Biopsy
Centrolobular Inflammation without Interface Hepatitis

Centrolobular inflammation:
66% AIH presenting as ALF
2002 AIH Treatment Goals
Definition of “Remission”

- Reduce mortality, symptoms
- Reduce AST and ALT to 1.5-2 X ULN
- Histology:
  - Confining inflammation to portal tracts
  - Eliminate interface hepatitis
  - Slow progression to cirrhosis
- Minimize immunosuppression to maintain “remission”
- Minimize serious adverse events
Probability of Cirrhosis During Steroid Therapy

Czaja A, 2003

During treatment
During follow-up
After treatment
2010 AIH Treatment Goals
New 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
Autoimmune Hepatitis
Frequency of Progression After “Remission”
Using Definition in 2010 AASLD Guideline

Lack of Progression During Remission
96%

Muratori L: Hepatology. 2011; 52: 1857
Autoimmune Hepatitis
Probability of Survival During Steroid Therapy

Czaja A, 2003
Autoimmune Hepatitis
Options for Immunosuppression

Immunosuppression Contraindicated
Absent/Minimal Disease Activity
Inactive Cirrhosis

Monitoring Every 3-6 Months

AIH Diagnosis Probable or Definite using IAIHG Diagnostic Scoring Systems

Induction Immunosuppression

AIH Excluded using IAIHG Diagnostic Scoring Systems

Continue Search for Diagnosis

Budesonide + Azathioprine
3 mg TID 1-2 mg/kg/d
Non-Cirrhotic Patients Only!

Monotherapy Prednisone (mg/d)

<table>
<thead>
<tr>
<th>Week</th>
<th>Prednisone (mg/d)</th>
</tr>
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<tbody>
<tr>
<td>Wk 1</td>
<td>60</td>
</tr>
<tr>
<td>Wk 2</td>
<td>40</td>
</tr>
<tr>
<td>Wk 3</td>
<td>30</td>
</tr>
<tr>
<td>Wk 4</td>
<td>30</td>
</tr>
<tr>
<td>Maintenance</td>
<td>20 and below</td>
</tr>
</tbody>
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Combination Prednisone+Azathioprine (mg/d)

<table>
<thead>
<tr>
<th>Week</th>
<th>Prednisone (mg/d)</th>
<th>USA (mg/d)</th>
<th>EU (mg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 1</td>
<td>30</td>
<td>50</td>
<td>1-2</td>
</tr>
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Autoimmune Hepatitis
Clinical, Biochemical and Histological Remission During Steroid Therapy

- Clinical Remission
- Biochemical Remission
- Histological Remission

Czaja A, 2003
Autoimmune Hepatitis
Prospective, Double-Blind, Randomized, Controlled Trial
Budesonide + Aza vs Prednisone + Aza

Autoimmune Hepatitis in Pregnancy

- Fertility due to secondary amenorrhea
- Treatment not contraindicated
- Prednisone alone safe
- Safety of prednisone + azathioprine less clear
- Risk to fetus
  - Prematurity (30%)
  - Low birth rate (35%)
  - C-section (26%)
- Risk of flare post-partum
- Complications of PVHTN due to expanded blood volume, intensified hyperdynamic circulation
Autoimmune Hepatitis
Relapse of AIH After Withdrawal of Therapy
Increased Probability of Cirrhosis and Need for OLT

Autoimmune Hepatitis
Alternative Immunosuppression to Achieve Remission

Responder
- Maintenance Therapy: Taper Off Prednisone
- Maintain Azathioprine
  - Remission: Normal ALT, IgG and/or liver histology
  - Withdraw Immunosuppression
  - Relapse
- Remission Maintained Monitor Closely

Non Responder
- Intolerance to Prednisone and/or Azathioprine
  - Verify Compliance
  - Optimise Immunosuppression with Prednisone and Azathioprine
- Failure to Achieve Remission: Abnormal ALT, increased IgG, or active liver histology
  - Alternative Therapies
    - Empiric Addition of:
      - Ursodeoxycholic acid
      - Mycophenolic acid
      - Cyclosporine
      - Tacrolimus
      - Sirolimus
      - Methotrexate
      - Rituximab

Budesonide + Azathioprine
- 3 mg TID 1-2 mg/kg/d
- Non-Cirrhotic Patients Only!

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<td>50</td>
<td>1-2</td>
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<td>1-2</td>
</tr>
<tr>
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<td>50</td>
<td>1-2</td>
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Autoimmune Hepatitis
Estimated Frequency of “Remission” Using 2002 vs. 2010 AASLD Guidelines’ Definitions

2002 AIH Practice Guideline: Remission 73% (27% Remission)

2010 AIH Practice Guideline: Remission 60% (40% Remission)

Muratori L: Hepatology. 2011; 52: 1857
- Foreign antigen
- Autoantigen
- Alloantigen

Cell Cycle Phase

G0 → G1 → S → Mitosis

Corticosteroids
Ursodeoxycholic acid
IVIG, HuOKT3, ALG, ATG
Hu-Max-CD4, Efalizumab, Enlimomab
Abetacept, Belatacept, Alefacept, Anti-CD154 (hu5C8)
Anti-CD137, Anti-CD4
Alemtuzumab

Azathioprine, 6-MP, 6TP
Mycophenolate mofetil
Leflunomide
FK778
IVIG, HuOKT3, ALG, ATG
Alemtuzumab

Sirolimus
Basiliximab
Daclizumab

Transendothelial Migration and Tissue Injury

Imflimixab
Adalimumab
Etanercept
Rituximab
Alemtuzumab

FTY720
Natalizumab
IVIG
Chemokine inhibitors

Vierling JM: Liver Immunology 2nd Ed, 2007
Mycophenolate Mofetil Treatment in AIH Patients Refractory or Intolerant to Conventional Therapy

Allopurinol to Optimize Thiopurine Metabolites in AIH

# Cyclosporine

<table>
<thead>
<tr>
<th>N</th>
<th>Regimen</th>
<th>Response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 patients</td>
<td>3 groups 2 CsA alone. 1 with steroids/AZA</td>
<td>100% remission</td>
<td>3 relapses – responded to CsA dose adjustment</td>
</tr>
<tr>
<td>32 patients</td>
<td>CsA 6 months AZA/Pred 1 month CsA stopped</td>
<td>100% remission</td>
<td>No relapses</td>
</tr>
<tr>
<td>19 patients</td>
<td>CsA 2-5mg/kg/d</td>
<td>Of the patients who continued therapy – 100% response</td>
<td></td>
</tr>
<tr>
<td>6 patients</td>
<td>CsA 3 mg/kg/d</td>
<td>5 of 6</td>
<td></td>
</tr>
<tr>
<td>6 patients</td>
<td>CsA 2-4 mg/kg/d</td>
<td>4 of 5</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Vierling JM, Flores PA. Clin Liver Dis; 2002(6): 825-850
Cyclosporine

Tacrolimus

ALT levels

P<0.05

Ishak score

Fibrosis score

P<0.05
Infliximab Rescue

Autoimmune Liver Diseases
Excellent Survivals Post-OLT UNOS Database


Figure 1. Post-OLT Patient Survival

- PBC ~12%
- PSC ~8%
- AIH ~6%*
- All Other ~74%
- AILDs ~26%

Patient Survival (%)

Years Post-OLT

0.0 0.2 0.4 0.6 0.8 1.0
1 2 3 4 5 6 7 8 9 10
Allograft Loss After OLT
Impact of Recurrent Diseases

Autoimmune Hepatitis Practical Summary

- Diagnosis of AIH based on inclusion AND exclusion of diseases mimicking biochemical, serological and histopathological features of AIH
  - Wilson disease
  - DILI
  - HCV infection without a positive anti-HCV
- Diagnosis aided by response to 4 week course of induction steroid monotherapy
- If AIH confirmed,
  - Convert to budesonide if non-cirrhotic
  - Add azathioprine: if intolerant to azathioprine, consider 6-MP or MMF
  - If generation of 6-TG inadequate, consider allopurinol
- If remission not achievable with steroids and azathioprine:
  - Switching azathioprine to mycophenolic acid futile
  - Alternative therapy with cyclosporine, tacrolimus, sirolimus, anti-TNFα agents
  - Role of ursodexoycholic acid unclear
- If remission achieved, continue maintenance therapy indefinitely