Autoimmune Hepatitis Treatment and Overlapping Syndromes

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Disclosures

• Grants
  • Allergan, BMS, Cymabay, Gilead, GSK, Intercept, Novartis, NGM, Shire, Takeda

• Consulting
  • Cymabay, Eli Lilly, GSK, Patara, Parvus, Pliant
Burden of AIH

- 49% with mild disease develop cirrhosis after 15 years
- Up to 20% do not respond or are intolerant to standard immunosuppression
- High rate of relapse (80%)
- Long term adverse events with medications
- *No new drugs developed for AIH in > 40 years*
Autoimmune Hepatitis

- Broad range from asymptomatic to acute/severe or even fulminant
- **Insidious onset** (most common clinical phenotype)
- **Acute onset** (about 25% of patients)
  - Acute exacerbation of chronic AIH
  - True acute AIH without histological findings of chronic liver disease
  - Centrilobular zone 3 necrosis (central perivenulitis) usually predominant
  - Autoantibodies or other classical features can be absent
- **Cirrhosis** present in ~1/3 of patients at diagnosis
HLA-DRB1*03:01 and HLA-DRB1*04:01
Odds Ratio (OR) for Risk: 2.9

Immune dysfunction in AIH

Abnormal immune profile does not change despite biochemical remission

AIH as an infectious disease

- German cohort of >300 patients
- Increase in frequency of anti-hepatitis E IgG among adults
- Children had higher frequency of parvovirus serologies.

### AIH - Diagnosis

**Feature/parameter** | **Discriminator** | **Score**  
--- | --- | ---  
**Antibodies (max 2 points)**  
ANA or SMA+  
ANA or SMA+  
LKM+  
SLA/LP+ | ≥1:40  
≥1:80  
≥1:40  
Any titre | +1  
+2  
+2  
+2  
(0–2 points total)  
**IgG or γ-globulins level**  
| >ULN  
>1.1 x ULN | +1  
+2  
**Liver histology**  
(evidence of hepatitis is required)  
Compatible with AIH  
Typical of AIH  
Atypical | +1  
+2  
0  
**Absence of viral hepatitis**  
| No  
Yes | 0  
+2  
---

Score ≥7 = Definite AIH  
Score ≥6 = Probable AIH

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AIH Histology

Plasma Cell Interface Hepatitis
Hepatocyte Rosettes
Emperiploids

Typical = All 3 features
Compatible = Chronic hepatitis without all 3 features

# AIH sub-types

<table>
<thead>
<tr>
<th>Sub-type</th>
<th>Features</th>
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</thead>
</table>
| AIH-1    | • Almost 90% of AIH cases  
• Detection of ANAs, SMAs or anti-SLA/LP  
• Any age at onset | • Usually excellent treatment response |
| AIH-2    | • Up to 10% of AIH cases  
• Anti-LKM1, anti-LC1 and rarely anti-LKM3  
• Onset usually in childhood/young adulthood  
• Clinical and histopathological severity commonly acute and advanced | • Sometimes failure of treatment and frequent relapse rates after drug withdrawal |
| AIH-3    | • Up to 10% of cases  
• Only SLA/LP positive  
• Otherwise very similar to AIH-1*  
• Often Ro52-antibody positive | • Lifelong immuno-suppression in most, if not all patients |

EASL CPG AIH. J Hepatol 2015;63:971–1004
Validation of HIP1R for the diagnosis of AIH

- Huntingtin-interacting protein 1-related protein (HIP1R)
- Better overall accuracy and specificity compared to ANA and SMA
- 177 untreated AIH patients vs 303 controls

<table>
<thead>
<tr>
<th></th>
<th>Anti-HIP1R</th>
<th>ANA</th>
<th>ASMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sens.</td>
<td>63.3%</td>
<td>70.2%</td>
<td>72.4%</td>
</tr>
<tr>
<td>Spec.</td>
<td>78.5%</td>
<td>49.1%</td>
<td>63.6%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>72.9%</td>
<td>57.6%</td>
<td>68.3%</td>
</tr>
</tbody>
</table>

AIH Diagnostic Challenges

- Seronegative AIH
- NASH with positive ANA
- DILI with or without ANA
- PBC Overlap
AIH and NASH

73 AIH patients

- 14% had AIH + simple steatosis
- 16% had AIH + NASH
  - 50% cirrhosis
  - 18% of AIH alone (p=0.032)

Drug-Induced AIH

Nitrofurantoin
Diclofenac
Minocycline
Interferon

AIH vs. Drug induced AIH

- Often there is less fibrosis (chronicity) on biopsy
- Usually resolves with drug discontinuation and can eventually remove steroids without relapse risk.

![Table 3. Comparison Between DILI/AIH and AIH Alone](resources/Table3.png)

AIH versus DILI

- 17 ANA+ DILI vs 167 AIH patients
- No difference in serum ALP, bilirubin, or GGT.
Probable or possible AIH vs DILI

0.5–1 mg/kg prednisone

Response

Taper steroids until withdrawal

Relapse

Definite AIH

Treatment of AIH

No relapse

DILI*

Avoid this drug in future

Non-response

Consider alternative diagnoses

EASL CPG AIH. J Hepatol 2015;63:971–1004
Overlap Syndromes

- 2-10% of autoimmune liver diseases have overlap
- May present sequentially or concurrently
- More difficult to manage clinically, more aggressive
PBC-AIH Overlap

- **AIH Score**
  - <1% of PBC patients meet definite criteria
  - 8-19% of PBC patients meet probable criteria
- **Simplified AIH Score**
  - Fewer overlap identified (4% versus 12%)
- **Paris Criteria**
  - ALT > 5 X ULN
  - IgG > 2 X ULN and/or ASMA+
  - Moderate to severe interface hepatitis

PBC-AIH Overlap

- ALT
- PBC
- AMA Prevalence
- PBC/AIH
- AIH
- AIH with AMA
PBC-AIH Overlap

AIH – When to Treat

- Advanced fibrosis/cirrhosis*
  - Treatment required
  - Induction therapy

- Active disease (HAI ≥ 4/18)
  - Treatment required

- Mild disease (ALT <3x ULN; HAI <4/18) and no advanced fibrosis
  - Treatment optional
    - Individual decision based on:
      • Age
      • Co-morbidities
      • Patient preference
      • Serology
  - If no treatment, monitor

*EASL CPG AIH. J Hepatol 2015;63:971–1004
AIH Remission

- Biochemical Remission
  - Normalization of ALT
  - Normalization of IgG
  - Low risk of significant activity on liver biopsy
- Histological Remission
  - Normal histology or HAI < 4
AIH – Treatment Failure

Higher all-cause and liver-specific mortality with increased histological activity index on follow up liver biopsy.
AIH - Treatment

Table 6. Immunosuppressive Treatment Regimens for Adults in Autoimmune Hepatitis

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
<th>Azathioprine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prednisone only* (mg/day)</td>
<td>Prednisone* (mg/day)</td>
<td>USA (mg/day)</td>
</tr>
<tr>
<td>Week 1</td>
<td>60</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Week 2</td>
<td>40</td>
<td>20</td>
<td>50</td>
</tr>
<tr>
<td>Week 3</td>
<td>30</td>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>Week 4</td>
<td>30</td>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>Maintenance</td>
<td>20 and below</td>
<td>10</td>
<td>50</td>
</tr>
</tbody>
</table>

Reasons for Preference

<table>
<thead>
<tr>
<th></th>
<th>Cytopenia</th>
<th>Postmenopausal state</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thiopurine methyltransferase deficiency</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
<td>Brittle diabetes</td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Short course (≤6 months)</td>
<td>Acne</td>
</tr>
</tbody>
</table>

*Prednisolone can be used in place of prednisone in equivalent doses.

### Budesonide vs. Prednisone

- **Randomized, placebo-controlled study in non-cirrhotic AIH**

#### Table: Study Protocol

<table>
<thead>
<tr>
<th>Segment A</th>
<th>Segment B**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>Week 5</td>
</tr>
<tr>
<td>Week 2</td>
<td>Week 6</td>
</tr>
<tr>
<td>Week 3</td>
<td>Week 7</td>
</tr>
<tr>
<td>Week 4</td>
<td>Week 8</td>
</tr>
<tr>
<td>Month 1</td>
<td>Month 2</td>
</tr>
</tbody>
</table>

**Segment B**

- Months 3 – 6
- Months 7 – 12

#### Budesonide group

- **Budesonide**
  - 3 mg TID
  - 3 mg TID, upon biochemical remission
  - 3 mg BID

- **Azathioprine**
  - 1 – 2 mg/kg BW/day depending on clinical judgement

#### Prednisone group

- **Prednisone high dose regimen**
  - 40 mg/day
  - Prednisone
  - 40 mg/day
  - 30 mg/day
  - 25 mg/day
  - 20 mg/day
  - 15 mg/day
  - 10 mg/day
  - 10 mg/day

- **Prednisone low dose regimen**
  - 40 mg/day
  - Prednisone
  - 30 mg/day
  - 25 mg/day
  - 20 mg/day
  - 15 mg/day
  - 10 mg/day
  - 10 mg/day

- **Azathioprine**
  - 1 – 2 mg/kg BW/day depending on clinical judgement

---

*Patients showing biochemical remission after 3 months of treatment could continue with Segment B after visit 4.

** Months 7 to 12: All patients received budesonide (3 mg TID/BID).*

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Budesonide vs. Prednisone

AIH

0.5–1 mg/kg prednisolone

Good response

Add azathioprine gradually up to 1–2 mg/kg

Azathioprine intolerance

Taper steroids*

Individualize doses to achieve and maintain normal ALT and IgG

Insufficient response

Consider non-compliance

Increase to i.v. 100 mg prednisolone

Response

Insufficient response

Refer to specialist centre for confirmation of diagnosis, LT evaluation and/or alternative immunosuppressives

Consider alternative diagnoses

Manage alternative disease

Good response

EASL CPG AIH. J Hepatol 2015;63:971–1004
Relapse in AIH

- Incidence of relapse or loss of remission
  - 59% after 1 year
  - 73% after 2 years
  - 81% after 3 years

- Combination therapy at start of withdrawal
  - Risk of relapse was higher
  - Time to relapse was shorter

Treatment Withdrawal

- Remission (normal ALT/normal IgG)
  - Reduce immunosuppression stepwise
    - Stable remission on monotherapy for >24 (36) months
      - Taper out immunosuppression completely (consider liver biopsy)
        - Stable remission without treatment
          - Monitor lifelong (3 monthly for 1 year, then 6 monthly)
    - Taper steroids, adapt azathioprine-dose (check 6-TG levels) as required to retain remission
      - Long-term (lifelong?) maintenance treatment
  - Relapse
    - Re-induce remission with prednisolone

EASL CPG AIH. J Hepatol 2015;63:971–1004
Acute Severe AIH

• 19% to 45% overall mortality
• 9% to 81% rate of liver transplant
• UK Series
  • 32 non-cirrhotic patients with INR $\geq$ 1.5
    • 23 treated with steroids ($\leq$ 40 mg/d)
      • 48% liver transplant
    • 9 patients untreated – all had liver transplant

“Difficult” to Treat

• 10–15% refractory to standard treatment
  • non-compliance vs true non-response
  • PSC or PBC overlap
  • Incorrect diagnosis
• “Incomplete” Response
  • reduction of ALT < 25% after 2 weeks
Incomplete Responders

- Check TGN levels
  - > 220 pmol/8 X 10^8 RBC
- Increase prednisone to 60 mg/d
- Consider alternate therapies
Alternative treatments

- 6-Mercaptopurine
- Mycophenolate Mofetil
  - Teratogenicity
  - GI side effects
- Tacrolimus
- Cyclosporine
- Infliximab
- Rituximab
What the Experts are Using
AIH – Alternative Agents

- Intolerance ($n = 108$)
  - Group 1
- Incomplete Response ($n = 93$)
  - Group 2

Rituximab for AIH

Than et al. ILC 2018 (poster Thu-202)
BAFF (B lymphocyte stimulator)

- Member of the TNF superfamily
- Cytokine is critical for the development, selection, and survival of mature B-cells
- The elimination of B-cells through BAFF-R therapy may also deplete T-cells populations, to negatively regulate T-cell-mediated immunity.

BAFF-R Ab in AIH

- **AMBER STUDY:** [VAY736](#) (lanalumab)
- Monoclonal Antibody against BAFF receptor
- Randomized, placebo-controlled, double-blind dose Phase 2/3 study in autoimmune hepatitis.
- Planned enrollment: 80 adults
- Incomplete responders to or intolerant of standard therapy
- S.C. every 4 weeks (three doses to be tested)
- Assessment at 24 weeks:
  - ALT normalization
Take Home Messages

• Diagnosis of AIH requires liver biopsy
• Most patients will achieve remission with standard treatment
• Effective options for drug intolerance, no for non-response
• Most patients will require life long treatment
• Minimize immunosuppression exposure
Muchas Gracias!