Autoimmunity and the Liver: Translation to the clinic

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Autoimmune Hepatitis

- **type 1:** adults and children
- **type 2:** mainly children
Autoimmune Hepatitis

Presentation

- adults: often chronic, mild/moderate severity
- children/young adults: often acute, aggressive
Juvenile Autoimmune Hepatitis

- type 1 (ANA/SMA positive): 2/3
- type 2 (LKM1 positive): 1/3
Juvenile Autoimmune Hepatitis

Similarities between Type 1 and Type 2 AIH

- females: 75%
- associated AI disorders: 20%
- family history of AI disease: 40%
- high IgG: 80%
Juvenile Autoimmune Hepatitis

Differences between Type 1 and Type 2 AIH

LKM1 positive AIH presents:

- at a younger age
- with partial IgA deficiency
- less frequently with cirrhosis
- more frequently with acute hepatic failure
Juvenile Autoimmune Hepatitis

~ 50% of children/adolescents with AIH-1 serology have an overlap syndrome with sclerosing cholangitis

Autoimmune Sclerosing Cholangitis
Autoimmune sclerosing cholangitis

Diagnostic Criteria

- high IgG
- autoantibodies (ANA/SMA)
- interface hepatitis
- abnormal cholangiogram

Gregorio et al, Hepatology 2001;33:544-553
**Autoimmune sclerosing cholangitis**

- affects equally males and females
- GGT and AP often normal at presentation
- particularly high IgG levels
- frequent positivity for ANCA
- frequently associated with IBD (sometimes asymptomatic)
**Juvenile Autoimmune Liver Disease**

**Diagnostic criteria**

- elevated transaminases
- exclusion of viral hepatitis, Wilson disease, NASH
- **positive autoantibodies**: ANA/SMA (titre ≥ 1:20) = **AIH-1** or **ASC**
  - anti-LKM1 (titre ≥ 1:10), anti-LC1 = **AIH-2**
- elevated IgG
- **liver biopsy**: interface hepatitis/multilobular collapse
- **cholangiogram** (MRCP, ERCP): normal = **AIH**; abnormal = **ASC**
Autoimmune Hepatitis

treatment
**AIH** – Definition of remission

- normal transaminase levels
- normal IgG levels

+ negative/<1:20 ANA/SMA
+ negative anti-LKM1

- adults
- children/adolescents
AIH – All presentations*
(excluding fulminant liver failure)

standard treatment:

- prednisolone
- azathioprine

* including acute liver failure with no or < grade 2 encephalopathy

fulminant liver failure ➤ transplant
Adulthood AIH

AASLD Guidelines

- 30 mg prednisone + 1–2 mg/Kg azathioprine/day

or

- prednisone monotherapy 40-60 mg/day

AASLD Guidelines, Hepatology 2010; 51:2193-213
Azathioprine can be *hepatotoxic*:
not advisable as first line Rx in ill, jaundiced patients particularly if cirrhotic
### Table 7. Treatment proposal for adult patients with AIH (e.g. 60 kg).

<table>
<thead>
<tr>
<th>Week</th>
<th>Prednisolone (mg/day)</th>
<th>Azathioprine (mg/day)</th>
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<tbody>
<tr>
<td>1</td>
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Reduction of prednisolone to 7.5 mg/day if aminotransferases reach normal levels and after three-months to 5 mg/day, tapering out at three-four months intervals depending on patient’s risk factors and response. *Azathioprine dose of 1–2 mg/kg according to body weight.
**Juvenile AIH**

Prednisolone

- 2 mg/Kg/day (maximum 60 mg/day)
- Gradually decreased over 4-8 weeks to 2.5-5 mg/day depending on age

+ UDCA if ASC
  (15 mg/Kg/day)
Juvenile AIH
Azathioprine

- **hepatotoxic**: never first line Rx in ill, jaundiced patients
- add if high steroid dose required to maintain normal or nearly normal AST or in the presence of serious steroid side effects
- **myelosuppressive**: start at low dose (0.5 mg/Kg/day) and increase gradually to 2 mg/Kg/day
Juvenile AIH

Rx schedule at King’s

‘Fine tuning’ to avoid severe side effects:

- weekly LFTs, INR, FBC
- aim to 80% AST decrease within 6 weeks
Juvenile AIH

80% ultimately require azathioprine
**AIH - Maintenance of remission**

**In adults:**

**In children:**
- successful in ANA/SMA+ AIH
- less successful in LKM1+ AIH
Juvenile AIH

King’s criteria for stopping treatment*

- **daily** treatment for at least **three years**
- at least one further year of **normal LFTs & IgG**, **negative or low titre autoantibodies** *(checked 3 monthly)*
- **no inflammation** on **liver biopsy** performed at the end of the year
- **gradual** discontinuation of azathioprine, then prednisolone

*never just before or during puberty*
AIH vs ASC

13-year (8-29) follow up – Transplant-free survival

Survival Plot (PL estimates)

survivors

P<0.009, Log Rank

Scalori et al, Hepatology 2007;46 Suppl 1:555A
### AIH vs ASC

**Outcome (King’s prospective study)**

<table>
<thead>
<tr>
<th></th>
<th>AIH-1</th>
<th>AIH-2</th>
<th>ASC</th>
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<tbody>
<tr>
<td>LT rate</td>
<td>6%</td>
<td>14%</td>
<td>27%</td>
</tr>
<tr>
<td>recurrence post LT</td>
<td>0%</td>
<td>0%</td>
<td>71%</td>
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*Gregorio et al, Hepatology 2001;33:544-553*

*Scalori et al, Hepatology 2007;46 Suppl 1:555A*
Autoimmune sclerosing cholangitis

King’s prospective study

progression of liver disease and recurrence post transplant are associated to active inflammatory bowel disease
Autoimmune Hepatitis

Alternative treatments

- for induction of remission
- for difficult-to-treat patients
Induction of remission

- 6-month CyA priming in AIH-1 followed by pred + aza: uncontrolled study, benefits unclear

- budesonide 3mg/tds + aza vs prednisone 40mg/od + aza

Alvarez et al, J Hepatol 1999;30:222
Budesonide - AIH

Multicentre European Study - Study design

azathioprine 1-2 mg/Kg  +

- **budesonide** 3 mg tds, decreased upon response

  versus

- **prednisone** 40 mg once daily reduced per protocol irrespective of response

- for 6 months, then budesonide to all for further 6 months

Manns et al. Gastroenterology 2010;39:1198-206
Woynarowski et al. J Pediatr;163:1347-1353
**Budesonide - AIH**

Definition of response

normal transaminase levels

without steroid side effects

Manns et al. Gastroenterology 2010;39:1198-206
Woynarowski et al. J Pediatr;163:1347-1353
Budesonide - AIH

European multicentre study - 203 pts

- budesonide: 60% remission
- prednisone: 39% remission

Manns et al, Gastroenterology 2010;139:1198-206
**Budesonide – Juvenile AIH**

Multicentre European Study
Paediatric cohort - 46 patients, 10-18 yr

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<tr>
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<tr>
<td><strong>Complete response</strong></td>
<td></td>
<td></td>
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<tr>
<td>6 months</td>
<td>16%</td>
<td>15%</td>
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<tr>
<td>12 months</td>
<td>50%*</td>
<td>42%*</td>
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* compared to ~90% with King’s protocol

Woynarowski et al. J Pediatr;163:1347-1353
Difficult-to-treat patients: resistant or unresponsive

- **MMF**
  - retrospective studies, more effective in *AIH* than in *ASC* [teratogenic!]
- **Calcineurin inhibitors**
- **Rituximab**
- **anti-TNFα**

*Aw et al, J Hepatol 2009;51:156*
Thank you
Adulthood AIH

EASL Clinical Practice Guidelines: Autoimmune hepatitis

- AIH
  - 0.5-1 mg/kg/d prednisolone
    - Good response
      - Add azathioprine gradually up to 1-2 mg/kg/d
        - Azathioprine-intolerance
          - Second-line therapy (usually MMF)
            - Taper steroids (ideally trial of steroid withdrawal)
              - Individualize doses (consider checking 6-TG levels) to achieve and maintain normal ALT and IgG
        - Insufficient response
          - Consider non-compliance
            - Increase to 100 mg prednisolone i.v.
              - Response
              - Insufficient response
                - Refer to specialist centre for confirmation of diagnosis, LTX-evaluation and/or alternative immunosuppressives
          - Consider alternative diagnoses
            - Manage alternative disease
Adulthood AIH

Diagnosis AIH

Advanced fibrosis/cirrhosis*  
Active disease (HAI ≥4/18)

Treatment required

Induction therapy

Mild disease (ALT <3x ULN; HAI <4/18) and no advanced fibrosis

Treatment optional, individual decision based on:
- age
- co-morbidity
- patient preference
- serology

If no treatment, monitor every 3 months (ALT, IgG); follow-up liver biopsy if there is increase of ALT and/or IgG

EASL Clinical Practice Guidelines: Autoimmune hepatitis™

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY
2015 vol. 63 | 971–1004
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