Autoimmune liver disease

- Autoimmune hepatitis YES
- Primary biliary cirrhosis YES
- Primary sclerosing cholangitis POSSIBLY

Autoimmune hepatitis

Autoimmune hepatitis is a rare disease in young/middle-aged women

No

Autoimmune hepatitis

Autoimmune hepatitis is a classical autoimmune disease

- T cell mediated destruction of hepatocytes
  - Immune recognition of specific liver antigens
    - Ya et al Gastro 2005
  - Loss of immune suppression defect in regulatory T cells
    - Longhi J 2006
- Hypergammaglobulinaemia
- Autoantibodies
- Female predominance (4:1)
- Response to corticosteroids (65%)
- Association with other AID/IBD

Autoimmune Hepatitis

- Prevalence 1:5,000 to 1:10,000
- Age 2 to 80 years
- 25% men
- Protean clinical manifestations

Autoimmune hepatitis presentation

- Acute hepatitis
  - Jaundice
- Chronic hepatitis
- Cirrhosis
- Abnormal liver tests on screening
  - Any elevation of liver enzymes could be due to autoimmune Hepatitis
- No single test will either diagnose or exclude AIH

IF TREATED EARLY PROGNOSIS EXCELLENT
**Diagnosis**

International autoimmune hepatitis working group

- Elevated transaminases
- Elevated IgGγ-globulins
- Autoantibodies (ANA, SMA, SLA/LP, LKM)
- Histology
  - Hepatitis
  - Interface activity
  - Plasma cells
- Absence of other diagnoses
  - Viral hepatitis


**Different types of Autoimmune hepatitis**

- Type-1 (SMA/ANA) most common
- Type-2 (LKM) more common in children adolescents
  - More aggressive
  - High probability of relapse on stopping treatment
- Type-3 (SLA+)
  - More likely to progress to cirrhosis
  - No known autoantibodies in up to 25%

**Autoantibodies in Chronic Hepatitis**

- AIH
  - SMA, ANA Type-1
  - LKM Type-2
  - SLA + others Type-3
  - none Ab negative

Lohse et al. Z. Gastro. 1995; 33: 1004

**Corticosteroids save lives in AIH**


**Treatment**

- AIH usually responds to immunosuppression
  - >90% patients go into remission
- Steroids drug of choice for remission induction
- Azathioprine drug of choice for maintenance
  - +/- low-dose prednisolone

Treatment

- Prednisolone 1mg/kg/day
  - Weekly reduction (by 10 mg steps) to 20 mg/d
  - Slower dose reduction to 10 mg/d
  - Reduction below 10mg/d once in biochemical remission

- Maintainance azathioprine 1 – 1.5 mg/kg

AIM: normal transaminases, normal IgG

Steroid withdrawal

- Should not be attempted before 12 months of treatment
- Risk of reactivation about 50%
- Risk of reactivation reduced by increasing azathioprine to 2 mg/kg

Complete treatment withdrawal in Autoimmune Hepatitis

- Relapse very common (75%)
- Almost INEVITABLE for type 2
  - Usually within 12 months after withdrawal
- Predicting relapse after withdrawal
  - Histological activity predicts relapse
  - >3 yrs stable remission predicts successful withdrawal
- Patients must be monitored closely after withdrawal

Need for follow-up biopsies?

- 5% per year progression to cirrhosis
  - Mayo Clinic Czaja et al.
- 25% of patients with normal transaminases have inflammatory lesions
- Normal IgG and normal transaminases best predictor of histological remission (> 90%)
- Confirmation of remission prior to a trial of treatment withdrawal
  Carpenter WR Clin Liver Dis. 2002

Treatment failure

- CHECK DIAGNOSIS and COMPLIANCE
- Repeat high-dose prednisolone
- Second line therapy
  - Mycophenolate
  - Tacrolimus or cyclosporin (only in experienced centres) use low dose to avoid nephrotoxicity
- Experimental
  - Biologics and novel immunosuppressants
    - Rapamycin
    - Anti-B cell therapy

On and Adams Hep Int 2011
**Budesonide**

Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis.

- Oral budesonide 3mg bd or tds in combination with azathioprine
- Induces and maintains remission in patients with noncirrhotic AIH
- Low rate of steroid-specific side effects.


**Cyclosporin or tacrolimus are effective alternatives to azathioprine**

- Specific inhibition of T cell activation mediated via calcineurin and NFAT activation
- Cyclosporin effective for maintenance
  - Alvarez et al. 1999 J Hepatol
  - Debray et al. 1999 J Pediatrics

Good second line option but use low-dose and monitor levels and renal function

**MMF as second line therapy in AIH?**

- Inhibit de novo purine nucleotide synthesis
- Arrest DNA replication in T and B lymphocytes

Mycophenolate mofetil for maintenance of remission in autoimmune hepatitis in patients resistant to or intolerant of azathioprine

- Paul D, Robakowski, Peter T, James, and Stephen D. Koller
- Zanzibar Medical Journal, 2002

Mycophenolate mofetil for the treatment of autoimmune hepatitis in patients refractory to standard therapy

- Devlin SM, Swain MG, Urbanski SJ, Burak KW
- Can J Gastro. 2004

MMF can effectively induce and maintain remission in refractory autoimmune hepatitis patients

**Hennes and Do et al Am J Gastroenterology 2008**

**Birmingham and Hamburg experience**

Data from two large specialized liver units to examine the possible role of MMF as second line treatment of AIH.

Out of 403 AIH patients
28 patients (20 women) failed on azathioprine/corticosteroids
- Persistent elevated transaminases > 2 times normal
- Could not tolerate azathioprine.

**Treatment Failure**

Gemma age 32

- 1997 presentation with acute hepatitis
  - Jaundice, malaise
  - SMA+ LKM- IgG 40g/l
  - Biopsy acute hepatitis plus plasma cells and interface activity consistent with autoimmune hepatitis

- 2 patients included due to MMF side effects
- 1 patient excluded due to noncompliance
- 44% effective
- 14% effective
• Treated with corticosteroids 40 mg/day
• Azathioprine added
• Settled
• Recurrent episodes of hepatitis
  – Transaminases up to 750 iu/l
• 2001 pregnant
  – Transaminases settle
• 2003-2005
  – Further flares

June 2005
• ALT 362 AST 313 IgG 32
  – Prednisolone 30 mg
  – Switched to cyclosporin

September 2005
• ALT 112 AST 85 IgG 17

September 2005
• PREGNANT

February 2006
  – 29/52 pregnant
  – ALT 33 AST 38 IgG 14.5
  – Prednisolone 10mg cyclosporin 175mg

• No control with
  – Azathioprine
  – Cyclosporin
  – Mycophenolate
  – Repeated cycles of prednisolone
  – Bx

Healthy baby delivered

IgG g/l

MMF
**Rituximab (anti-CD20) in autoimmune hepatitis?**

- Autoantibodies are characteristic of AIH
- B cells & plasma cells detected within the liver
- B cells drive liver fibrosis in animal models
- Used to treat cryoglobulinaemia
  - autoimmune hepatitis
  - chronic HCV infection
- Relatively safe
  - Reactivates HBV

**Autoimmune hepatitis and pregnancy**

- AIH affects women of childbearing age
- Pregnancy safe in well-controlled AIH including cirrhosis
- Pregnancy associated immune tolerance
  - Aluvhare Nat Imm 2004
- Monitor closely during pregnancy and postpartum
  - Post-partum flares
- Corticosteroids, azathioprine and cyclosporin (if carefully monitored) are safe in pregnancy
- Avoid mycophenolate


**Relapse in autoimmune hepatitis**

- 2000 16 year old boy
- Acute hepatitis
  - ANA+ 1:1600; IgG 27;
  - interface hepatitis plus plasma cells
- Type 1 AUTOIMMUNE HEPATITIS

- Started on aza and prednisolone
  - responded
**Autoimmune Hepatitis**

- Plasma cell rich portal inflammation

**Relapse in autoimmune hepatitis**

- 2003
  - AST 36; IgG 15
  - Diarrhoea investigations show mild pancolitis

- 2006
  - Itching, malaise
  - AST 185; bilirubin 18; IgG 28
  - Insists he is taking his medication

**LIVER BIOPSY**

- Biopsy
  - Biliary hepatitis
  - Bile duct inflammation
  - Bile ducts absent from 25% of portal tracts

- MRI cholangiogram
  - Beading and strictures
  - ?primary sclerosing cholangitis

- He has progressed from AIH to PSC

**AIH progressing to PSC in adults**

  - Typical biochemical, serological & histological features of AIH at presentation
  - Most have inflammatory bowel disease
  - Initial response to immunosuppressive therapy
  - Subsequently progressive biliary disease, with cholangiographic features of PSC (time interval up to 14 years)

**Extraintestinal Manifestations of inflammatory bowel disease**

- **Eye**
  - Uveitis
  - Iritis
  - Episcleritis

- **Joints**
  - Type 1 and 2 Arthropathy
  - Orchard, Wootonworth and Jewell
  - Ankylosing spondylitis

- **Skin**
  - Erythema Nodosum
  - Pyoderma Gangrenosum

- **Liver**
  - Primary sclerosing cholangitis
  - Autoimmune hepatitis
  - 3-10% of patients with UC
  - 1-2% of patients with CD

**PSC may be preceded by autoimmune hepatitis**

Particularly in the context of IBD

Corticosteroid response lost as disease progresses

Broome U et al Gut 1996
Chapman, R.W. Gut 1991
Unresolved issues

• What is the best immunosuppressive treatment?
• When can we stop treatment?
• One disease with protean presentations or several similar diseases?
  – What are the triggers?
  – What determines severity of outcome?
  – Is AIH associated with IBD a different disease?
• What are the underlying mechanisms that allow a breakdown in self-tolerance?

Overlap Syndromes in Autoimmune Liver Disease
Patterns of Presentation

1. “True” overlap syndrome
   features of PBC or PSC and AIH at same time

2. “Sequential” Syndrome
   initial presentation with features of one disease
   - subsequently develop features of another disease

Distinct diseases with overlapping biochemical, serological or histological features
• Co-existent autoimmune disease related to shared genetic susceptibility
• Continuous disease spectrum with different manifestations
Inflammatory bowel disease & liver disease

- Primary sclerosing cholangitis or autoimmune hepatitis develop in
  - 3-10% of patients with UC
  - 1-2% of patients with CD
- 70% of patients with PSC suffer from IBD
  - Broome et al Dis Colon Rectum 1995
  - Loftus Gut 2005
- PSC can develop after colectomy for UC
  - Broome et al Gut 1996
  - Loftus et al IBD 1997

Liver disease runs a course that is independent of bowel disease

Diseases associated with active bowel disease