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# Autoimmune Liver Disease Update 2014

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# Disclosure

- Dr. Peters has disclosed that her spouse is an employee of Hoffman La Roche.

# Pathogenesis of Autoimmune Diseases

**Genetics**

- HLA
- Immunoregulation
- Other AI diseases
- 50% explained

**Environment**

- Infections
- Xenobiotics
- Hepatic micro-environment

# Autoimmune Hepatitis

- Autoantibodies
- Hypergammaglobulinemia
- Histology: plasma cells and interface hepatitis on biopsy, cirrhosis up to 40%
- Females: bimodal age distribution
- Often Family history of autoimmunity
- HLA association: A1-B8-DR3 haplotype

# Title: Histological Changes That Reliably Differentiate Autoimmune Hepatitis from Drug-Induced Autoimmune Hepatitis: Important Role of Liver Biopsy??

**AIH versus AIH-DILI**

13 AIH-like DILI, 10 female, 3 male, 50 y (range 22-73)

- herbal medications (3), one each infliximab, fenofibrate, statins, INH, ART, phenobarbital, moxifloxacin, azathioprine, sertraline and polypharmacy
- Controls: 16 cases, 8 males, 8 fem, 51 y (range 19-59

AASLD S. Dhingra Mount Sinai, New York poster #1059

# Title: Histological Changes That Reliably Differentiate Autoimmune Hepatitis from Drug-Induced Autoimmune Hepatitis: Important Role of Liver Biopsy??

## AIH versus AIH-DILI

- More common in AIH DILI venulitis, either portal or central or both, presence of ceroid macrophages, lobular disarray and panacinar necrosis and ballooning degeneration
- No difference between presence and number of plasma cells, confluent necrosis, and interface hepatitis, or classic histological features of AIH

AASLD S. Dhingra Mount Sinai, New York poster #1059

# Title: Can a dietary supplement induce autoimmune hepatitis?

35 cases DILI OxyElite Pro New Formulation –

- weight-loss supplement
- 2 OLT, 2 died, 25 recovered
- 4/6 chronic- liver biopsy- c/w AIH
  - 6 steroid responsive
  - 2/6 definite, 3/6 probable

# Autoimmune Hepatitis: Diagnosis

## Positive

- Female (4-6:1)
- High AST: Alk Phos
- High globulins
- AutoAb +
- Viral hep neg
- Drug history negative
- ETOH low
- Other Autoimmune dz
- HLA haplotypes
- Response to Rx

## Negative

- High Alk Phos: AST
- Viral serology +
- Drug history +
- ETOH high
- Bile duct damage
- Positive AMA

# AIH Criteria: >15 AIH; 10-15 probable

| Score | +3 | +2 | +1 | -2 | |
|---|---|---|---|---|---|
| **Gender** | | fem | | | |
| **Alk P:AST** | | <1.5 | | >3 | |
| **Globs** | **>2** | >1.5 | >1.0 | | |
| **ANA** | **>80** | 80 | 40 | | |
| **AMA+** | | | | | -4 |
| **Vir Hep** | Neg | | | | -3 Pos |
| **AIDz** | | Y | | | |
| **Biopsy** | PMN | | rosetting | biliary | |

AIHG 1999

| Variable | Cut off | Points | Cut off | Points |
|---|---|---|---|---|
| ANA or SMA* | ≥ 1:40 | 1 | ≥ 1:80 | |
| LKM | | | ≥ 1:40 | 2 |
| SLA | | | positive | |
| IgG | >ULN | 1 | >1.1 x ULN | 2 |
| Histology | Compatible with AIH | 1 | Typical of AIH | 2 |
| Absence of viral hepatitis | | | yes | 2 |
| | **Probable AIH*** | **6** | **Definite AIH*** | **≥ 7** |

Hennes *Hepatology* 2008

# Non-classical autoantibodies in Autoimmune Hepatitis and Overlapping Syndromes (OS): Do they contribute any relevant information?

- ANA, SMA LKM-1 are classically diagnosis and classification
  - not good as prognostic markers during follow-up
- Anti- soluble liver antigen (anti-SLA), anti-Ro-52, anti-liver citosol (anti-LC1), anti-Sp100 and anti-gp210
- Type I AIH in 88% and OS in 12% of 130 patients
  - ANA (73%), SMA (55%). Ro52 (37%), SLA (19%)

# Non Classical AutoAntibodies in AIH

- 130 pts: Classic: 91% fem; 73% ANA; SMA 53%
- Ro52 (Trim21) 37%; SLA 19%
- Ro52: lower ALT Resp; lower fibrosis; trend to more AIDz
- Anti-SLA -lower ALT response (48% x 74% p 0,014)

# Non Classical AutoAntibodies in AIH

- anti-Sp100 and anti-gp210 related to older age (45±18 x 32±17 p 0,04 to Sp100 and 42±18 x 32±17 p 0,04 to gp210) and overlap (56% x 10% p 0,002 to anti-Sp100 and 40% x 9% p 0,005 to anti-gp210)
- Anti-LC1 more frequent with ALF (67% x 29% p 0,07)
  - higher gammaglobulin levels (3,9 ±1,4 x 2,8 ±1,2 p 0,06)

# AIH

| Type | Antibody | Antigen |
|---|---|---|
| Type I | ANA | nuclear antigens |
| | SMA | F actin (20% not- so need IFL) |
| severe | SLA/anti-LP | UGA repressor |
| | | tRNA assoc protein |
| Type 2 | LKM | Cyp 2D6 |

- Not liver specific; 95% AIH-1 + for ANA/SMA
- anti-F-actin antibodies in 75% AIH-1 but 24% AIH-2, PBC, PSC, viral hepatitis and celiac disease
- SMA less sensitive but more specific than F actin

Bogdanos et al: Seminars in liver disease (2009)

# Predictors of AIH in HCV Overlap or Induction?

- Database of 787 HCV with >=1 ANA tested
  - Mean age 44 years, 59% male, 69% Cauc, 19% AA
  - 62% (n=483) HCV alone,
  - 36% (n=289) HCV+ANA+
  - 2% (n=15) had HCV/AIH
    - female (73%), ANA+ (87%), ASMA+ [33% (3/9)], anti-LKM+ [50% (4/8)] and 13% (n=2) post interferon use
    - higher serum ALT, IgG levels, globulin fraction and greater periportal HAI scores on biopsy (p<.05)

AASLD Kim NIH #36- database study

# Predictors of AIH in HCV Overlap or Induction?

- MV predictors of HCV/AIH were
  - ANA positivity, female sex,
  - higher HCV RNA,
  - Higher ALT and globulin fraction.
- 11 matched Bx: only diff was HAI score, not plasma cells, rosette, perivenular necrosis

AASLD Kim NIH #36- database study

# AIH: Treatment

- Prednisone 30-60 mg per day: 2mg/Kg/d
  - If normal ALT Decrease 10 mg per week till 30 mg
  - Decrease 5 mg/ 2-4 weeks
  - Monitor LFT's before every drop
- Budesonide 3 mg tid
- Azathioprine 1-1.5 mg /kg /d – check TPMT

# AIH: Treatment

- Maintenance
  - Monitor LFTs and CBC 3 monthly
- Remission: clinical, biochemical, histological
  - 65% achieve remission by 18 mos, 80% by 2 y
- 50-86% relapse after withdrawal of Rx
- Alternative medication: cell cept, FK, CSA- need to balance benefit with S/E- consider OLT

# Budesonide vs Prednisone in AIH

- Primary endpoint Normal ALT without steroid side effects:
  - in 47/100 patients on budesonide (47.0%)
  - in 19/103 patients on prednisone (18.4%, P < .001)
- At 6 months, complete biochemical remission occurred in 60% budesonide versus 38.8% in prednisone (P = .001)

Manns *Gastro* 2010

# Budesonide vs Prednisone in AIH

- Side effects in 28.0% budesonide group versus 53.4% prednisone group ($P < .001$)
- Among 87 patients who were initially given prednisone and then received budesonide after 6 months, steroid-specific side effects decreased from 44.8% to 26.4% at month 12 ($P < .002$)

Manns *Gastro* 2010

# AIH: Treatment Alternative Medications

- Mycophenylate mofetil 1 g bid- alternative to azathioprine no RTC
- FK- 9 pts on low dose FK able to decrease pred dose and improve histology- Larsen WJG 2007
- CSA >100 pts studied in small trials- lab and histological benefit – 100-300 mg trough levels
- Deflazacort- oxazoline derivative of pred less complications
  - maintained remission in 15 pts (7.5 mg = 5mg pred)
- Rituxamab- case reports in assoc with AI hemolytic anemia- Santos Liver Internat 2006
- Need to balance benefit with S/E- consider OLT

# Long Term Follow-up and 10-year Outcomes of Second-line Therapy in Autoimmune Hepatitis Klintman #324

- 23 patients diagnosed with AIH 1988-2009 and treated with tac (11) and/or MMF (12) for 10 y in UK
- intolerance (n=12) or response failure (n=11)
- complete response 39%, PR or RR 48%
- no difference in response between the tac and MMF group (p>0,05)

# Long Term Follow-up and 10-year Outcomes of Second-line Therapy in Autoimmune Hepatitis Klintman #324

- F/U: 14/15 with no OLT in remission, 7/15 were taking MMF and/or tac and 8/15 steroids ± AZA
- 6/23 (26%) OLT at a median of 7,5 years (4-19)
  - 3/6 had suboptimal adherence to medication vs. 1/17 in the non-transplant group (p<0,01)
  - 2/6 had multiple side effects limiting treatment options
- Conclusion: MMF tacrolimus are options

# Autoimmune Hepatitis

- May be induced by drugs
- May co-occur with other diseases e.g. HCV, DILI
- Autoantibodies -new ones may reflect heterogeneity
- Hypergammaglobulinemia
- Histology:
  - plasma cells and interface hepatitis on biopsy, cirrhosis up to 40%
  - May not be diagnostic
- Budesonide should be first line in non cirrhotics
- Other IS not studied in RTC but are alternatives

# Sub-stratification of hepatocellular carcinoma risk in men with PBC: results of an international multicenter study

- 4565 patients with confirmed PBC (median follow-up 7.1 years)
- 123 cases of HCC
- Men more likely to develop HCC (incidence rate: 6.7 vs. 2.6 cases per 1,000 patient years; HR: 2.91, 1.9-4.8 $p<0.0001$)

AASLD Trivedi for 15 North American and European liver centres #281

# Sub-stratification of hepatocellular carcinoma risk in men with PBC: more HCC in men

- Significant with advanced disease at PBC diagnosis (HR 2.9, 95% CI 1.60-5.32, p<0.001) not early F
- NS between genders in patients with early-stage PBC (p=0.49)
- Those on UDCA was similar in men and women
- Highest risk: NR male; male-responders worse than female non-responders (overall log-rank p<0.001)

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# Risk Stratification in Primary Biliary Cirrhosis Using the UK-PBC Research Cohort

- Time-to-event analysis (Cox prop hazard regression model)
- Entry point date of presentation, endpoint date of ‘failure’ (OLT, death from PBC-related liver failure)
- 2274 PBC patients treated with UDCA for at least one year

# Risk Stratification in Primary Biliary Cirrhosis Using the UK-PBC Research Cohort

- MV liver biochemistry after one year of UDCA most strongly predicted failure
  - bilirubin(P=1.31x10-19),
  - transaminases(P=1.92x10-12)
  - alkaline phosphatase(P=0.003)

# Risk Stratification in Primary Biliary Cirrhosis Using the UK-PBC Research Cohort

- Variables reflecting disease stage had effects independent of UDCA response, i.e. baseline bilirubin (P=0.0002), creatinine (P=0.0102), albumin (P=0.0001), platelet count (P=0.0006) and splenomegaly (P=0.0005)
- Treatment of PBC should be guided by the biochemical response.
- Risk assessment might be improved by taking the stage of the liver disease into account

AASLD 2014 Carbone #303

# Efficacy of Obeticholic Acid in Primary Biliary Cirrhosis as Assessed by Response Criteria Associated With Clinical Outcome: A Poise Analysis

- OCA ±UDCA (stable, continuing dose) if ALP≥1.67xULN or bilirubin <2xULN
- Randomized to PBO, OCA 5 (to 10 mg at 6 mos) or 10 mg for 12 mo

- Paris I, ALP ≤ 3x ULN and AST ≤ 2x ULN and Total Bili ≤ ULN
- Paris II, ALP ≤1.5x ULN and AST ≤1.5x ULN and Total Bili ≤ ULN
- Rotterdam bili and albumin Normal: Moderate: abnormal bili or albumin; Severe: Both bilirubin and albumin abnormal
- POISE Endpoint: Patients with ALP <1.67xULN, ≥15% ALP reduction and normal bilirubin
- Pruritus decreased when OCA titrated up: 58% vs 70% in 10 mg OCA

AASLD 2014 Luketic #309; international study; Bowlus #305

# Efficacy of Obeticholic Acid in Primary Biliary Cirrhosis as Assessed by Response Criteria Associated With Clinical Outcome: A Poise Analysis

| Rx (n) | Poise end | Paris I/II start | End Paris I/II |
|---|---|---|---|
| Placebo (73) | 10 | 53/ 0 | 48 4 |
| OCA 5→10mg (70) | 46* | 49/ 0 | 79*** 27** |
| OCA 10mg (73) | 47* | 52 0 | 70*** 26** |

OCA vs. Pbo: *p<0.0001, ** p<0.001, ***p<0.02

- No significant changes according to the Rotterdam criteria, ?due to the high percentage of normal bili alb patients (81%)
- side effect pruritus 10%

ALT AST bili

**Kowdley #319** extended 28pts to 3.5y safely continued efficacy (30-40, 12%)

AASLD Luketic #309 Trivedi for 15 North American and European liver centres #281

# Assessment of Environmental Exposures among 1000 North American Primary Sclerosing Cholangitis Patients with and without Inflammatory Bowel Disease

- Case-control analysis between 1000 cases 663 controls adjusted for age and gender 741 with IBD 259 without IBD.
- Smoking inversely associated with PSC only when IBD present (OR, 0.5; 95% CI 0.4- 0.7) but not among PSC patients without IBD (OR, 0.9; 95% CI 0.7-1.2).
- Women with PSC (irrespective of IBD) less likely to have HRT (OR, 0.5; 95% CI 0.4-0.7) more likely to have recurrent UTI's (OR, 1.6; 95% CI 1.2-2.3)
- PSC patients regardless of gender or IBD status were less likely to eat fish (OR, 0.4; 95% CI 0.3-0.6), vegetables (OR, 0.9; 95% CI 0.8-0.9) and grilled/barbecued meat (OR, 0.8; 95% CI 0.7-0.9). PSC patients more likely to consume steak/burgers that were more well-done (OR, 1.3; 95% CI 1.2-1.5).

Eaton AASLD #292

# Efficacy Trial of All-trans Retinoic Acid (ATRA) in Combination with Ursodeoxycholic Acid (UDCA) in Primary Sclerosing Cholangitis (PSC) ?? alternative

- ATRA activate FXR (farnesoid X receptor) and RXR (retinoid X receptor) and repress CYP7A1 and bile acid synthesis in human hepatocytes
- 45 mg/m2/day with UDCA mean 18±6 mg/kg/day 12 wks
- Mean AP (356±209 vs. 318±225 U/L, p=0.046); 20% achieved ≥30% reduction
- Mean ALT declined (94±55 vs. 56±32 U/L, p=0.007)

# Efficacy Trial of All-trans Retinoic Acid (ATRA) in Combination with Ursodeoxycholic Acid (UDCA) in Primary Sclerosing Cholangitis (PSC) ?? alternative

- Serum bile acid levels (41±52 vs. 28±45 umol/L, p=0.04)
- Mean LDL (131±60 vs. 155±51 mg/dL, p=0.055) and triglyceride (86±31 vs. 145±45 mg/dL, p=0.003) levels increased while HDL decreased (61±21 vs. 41±11 mg/dL, p=0.01)
- Mean serum levels of bile acid intermediate 7a-hydroxy-4-cholesten-3-one (C4) significantly decreased (17±19 vs. 9±11 ng/mL, p=0.04)
- S/E headache (63%) and tinnitus (26%)

# PBC and PSC new information

PSC

- HCC can occur in PBC especially men
- Alk Phos response 1 y predicts outcome
- OCA most useful in early disease, dose limited

PSC: early data on possible new therapy- all trans retinoic acid