Primary Biliary Cirrhosis : NOT ANY MORE!!
PRIMARY BILIARY CHOLANGITIS

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I will be discussing off label/investigational uses of silymarin and fenofibrate for primary biliary cholangitis.

1851, Addison and Gull described the clinical picture of progressive obstructive jaundice in the absence of mechanical obstruction of the large bile ducts.

1950, Ahrens and colleagues named this disease primary biliary cirrhosis.

PBC
• Middle-aged women
• Autoimmune disease (Presumably)
  – genetic predisposition
  – environmental triggers
• Interlobular – septal:
  – inflammatory ductular destruction
• Rising incidence and prevalence

PBC - Epidemiology
• Female: male 9:1
• Median age of onset: 50 (21 – 91)
• 19 – 240 cases per million
• PBC in relatives (HLA-DR8)
• Affects about 1/1000 women age >40 years and is a leading indication for liver transplantation in that population
On the rise?

- variety of environmental toxins
- infectious agents,
  - including viruses, bacteria, and chemicals,
- may trigger an immune response that becomes self-perpetuating.
- Genetic susceptibility
  - increased frequency of PBC among first-degree relatives of index patients and by the association with certain HLA haplotypes

PBC – Pathogenesis

- Immune response (CD4, CD8)
  - Allo-antigen (?)
- Progressive bile duct destruction
- Cholestasis
- Biliary Cirrhosis

• AMA: PDC-E2
  - BC01
  - AC01
  - E2
  - Protein X

PBC – Clinical

- Asymptomatic
  - 30%
- Symptomatic
  - Fatigue/Pruritus: 70%
  - Hepatomegaly: 50%
  - Splenomegaly/Jaundice: 30%
  - Xanthelasma: 30%

PBC - Clinical

- Associated Diseases
  - Keratoconjunctivitis sicca: 72-100%
  - Arthritis/Arthropathy: 4-42%
  - Scleroderma: 15-20%
  - Thyroiditis: 15-20%
  - Cutaneous disorders: 11%
  - RTA: 50-60%

PBC: Diagnosis

- Biochemical results: cholestasis
  - ALK phos: 3-4x, mild AST/ALT
  - Normal bilirubin (early)
- AMA positive: 95%
  - M2
  - ANA in 35%, ASMA in 66%, RF: 70%
  - Elevated IgM
- ANA gp 210
- Anticentromere
- Biopsy
Diagnosis

• Unexplained elevation of ALP ≥ 1.5x ULN
• Positive anti-mitochondrial antibody
• Non-suppurative destructive cholangitis on histology

• Two out of these 3 criteria are required

To biopsy or NOT to do it?

If:

– AMA
– Alk Phos > 1.5 times nl
– AST < 5 times normal

Then:

– Positive predictive value for PBC > 98%
  • (sensitivity 80%, specificity 92%)

Zein CO, Angulo P, Lindor K. When is liver biopsy needed in the diagnosis of primary biliary cirrhosis? Clin Gastro and Hepatol 2003;1(2):89-95

PBC and elastography

Survival according to baseline LSM

PBC: NATURAL HISTORY.

A) Asymptomatic PBC.

• +AMA and normal LFTs: very early PBC
• +AMA and abnormal LFTs: survive longer but life expectancy is still < age & gender-matched population
• 40% of asymptomatic pts: symptoms of PBC within 5-7 y
• Once symptoms develop: median survival 10 y

PBC – Natural History

• Asymptomatic

  Follow up: 17.8 yrs
  83% abnormal enzymes
  76% symptoms
  4+10 disease progression
  No evidence of liver related death

  Abnormal enzymes → 40% symptoms (5-7 yrs) → 10 yr survival

Metcaif, Lancet 1996 348:399

B) Symptomatic Disease.

• More rapid progression to ESLD and worse prognosis
• Independent predictors of poor prognosis: adv age, bil, poor synthetic function, hepatomegaly, fluid ret variceal bleeding and adv histol stage
• PHN and its complications: similar to other forms of cirrhosis:
  - PHN can be found in pts without cirrhosis
  - E. Varices:33% of pts with PBC
  40% variceal bleeding within first 3 y

PBC: NATURAL HISTORY.
PBC - Clinical

- Symptomatic
  - Age
  - Bilirubin level (>10 → 2 yr)
  - Albumin
  - Fluid retention (edema, ascites)
  - Variceal bleeding (30% varices → 40% bleed)
  - Advanced histologic stage

### Table 1. Histologic Staging of Primary Biliary Cirrhosis.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Histologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Inflammation in the portal space</td>
</tr>
<tr>
<td>II</td>
<td>Inflammation extending into the hepatic parenchyma</td>
</tr>
<tr>
<td>III</td>
<td>Septal or bridging fibrosis</td>
</tr>
<tr>
<td>IV</td>
<td>Cirrhosis with regenerative nodules</td>
</tr>
</tbody>
</table>

PBC: Inflammation to fibrosis

![Histologic Staging Images]

| Table 4 - Independent Predictors of Survival in Patients with Primary Biliary Cirrhosis |
|---------------------------------------------------------------|---------------------------------|
| Yale (%) | European (%) | Mayo (%) | Oud (%) | Glasgow (%) | Australian (%) |
| Age | Age | Age | Variceal bleeding | Age | Age | Age |
| Biliary | Biliary | Biliary | Biliary | Biliary | Ascer | Biliary |
| Strongly | Albumin | Albumin | Albumin | Albumin | Albumin | Albumin |
| Fibrosis | Cirrhosis | Proliferative time | Biliary | Proliferative bleeding | Fibrosis | Cholestasis | Makary's bodies |
| Cholestasis | Cholestasis | Biliary | Biliary | Biliary | Biliary | Biliary |

PBC: Inflammation to fibrosis

**PREDICTING SURVIVAL IN PBC**

- Without Tx course extends over 15-20 year period
- T bil>10mg/dl:average life expect reduced to 2 y
- To predict survival, several prognostic models:
  - Mayo risk score widely used:
    + in predicting survival
    + in guiding physician in pt referral for OLT
    + to monitor effect of experim drugs in clinical trials.
Risk stratification
• Various response criteria
  – Barcelona, Paris, Rotterdam, Toronto, Mayo
  • Based on dichotomization of a continuous variable (ALP, AST, TB, albumin)
  – APRI
• Mathematical models
  – More sophisticated modeling of several variables
    • Mayo Risk Score
    • Globe PBC score
    • UK-PBC score

GLOBE Score: Online Calculation

Therapeutic Options
– Corticosteroids
– D-Penicillamine
– Colchicine
– Azathioprine
– Chlorambucil
– Cyclosporine
– Methotrexate

Future promises?
• Bezafibrate/Fenofibrate
• Silymarin
• B cell antibodies
• FXR agonists

Therapeutic Implications
• Ursodeoxycholic Acid
  – Replaces toxic hydrophobic bile salts
  – Prevents extraction of membrane lipids by more hydrophobic bile salts.
  – More hydrophilic bile is less toxic to biliary epithelium.
  – Down regulates expression of MHC-I
  – Increases canalicular bile salt excretion
  – Stimulates chloride secretion
URSO
13-15 mg/kg/d
• 30 – 60% of bile acids on Rx
• Improves liver biochemistries and histology.
• Delays progression to cirrhosis.
• Improves survival free of liver transplantation.

[Image: Gastro 1997; 113:884-890]

URSO PANACEA OR PLACEBO?


• Meta-analysis that was confined to trials:
  – using an appropriate dose of ursodeoxycholic acid (>10 mg per kilogram of body weight per day)
  – and with sufficient follow-up (at least 2 years)
  – included a total of 1038 patients (522 who received ursodeoxycholic acid and 516 who received placebo).
• Treatment with ursodeoxycholic acid resulted in significant improvement in liver biochemical values.

Am J Gastroenterol 2006;101:1529-1538

ALP <1.67 x ULN and Normal Bilirubin after 1 Year of UDCA is Highly Predictive of Outcome


Patients Who Are Diagnosed and Treated Earlier Have Increased Event-Free Survival


UCDA improved:
• liver biochemistry
• but not symptoms or the progression of histological stage
Meta-analysis showed no difference
• in the incidence of death (odds ratio 1.21, 95% CI 0.71-2.04)
• liver related death (0.72, 0.22-2.32),
• liver transplantation (1.72, 0.78-2.07),
• death or transplantation (1.26, 0.87-1.82)
• in complications of liver disease (1.11, 0.64-1.92).
Interpretation: Published randomised controlled trials of UDCA do not show evidence of therapeutic benefit in PBC and its use as standard therapy needs to be re-examined.

UDCA

- Safe, may improve clinical symptoms, delay progression of disease and survival, and improve QOL
- However, up to 40% of PBC patients treated with UDCA have a suboptimal response

PBC: COMBINATION THERAPY.

- UDCA+Methotrexate
- UDCA+Colchicine
- UDCA+Corticosteroids
- UDCA+Prednisone+Azathioprine

These combinations do not seem to be more effective than UDCA alone.

Fenofibrate for PBC

Some biochemical benefit in the short term

Silymarin

- 27 patients with suboptimal response to UDCA (13-15 mg/kg/day)
- No change in Alk Phos, AST, Bilirubin, Albumin, or Mayo Risk Score

Obeticholic acid
Obeticholic acid

POISE titration at 6 months: Subjects in OCA titration arm titrated from 5 mg to 10 mg at Month 6 if they met any of the following criteria at the Month 6 assessment:

• The primary endpoint (ALP < 1.67xULN or bilirubin ≤ ULN) was not achieved
• No evidence of tolerability issues, e.g. pruritus

Placebo (n=73)
OCA 10 mg (n=73)
OCA 5 mg

Screening
OCA 5-10 mg dose adjustment option

Months in Open-Label Phase

POISE: Primary composite endpoint in the double-blind and open-label extension phases

1 endpoint: ALP < 1.67xULN, with a reduction of at least 15% from BL, and a total bilirubin < ULN

POISE: Alkaline Phosphatase levels in the double-blind and open-label phases

Alkaline Phosphatase levels in the double-blind and open-label phases

POISE: Total bilirubin levels during the double-blind and open-label phases

Total bilirubin levels during the double-blind and open-label phases
Adverse Events in POISE and Open-Label Extension

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=73)</th>
<th>OCA 5 -10 mg (N=70)</th>
<th>OCA 10 mg (N=73)</th>
<th>Open Label (N=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAE</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>


PBC: COMPLICATIONS OF CHRONIC CHOLESTASIS AND MANAGEMENT.

1) Bone Disease.
- Exercise and supplemental Ca+vitam D(25-50000 IU 2-3x week).
- Estrogens: use cautiously in pts with cholestasis
- Raloxifen: selective estrogen-receptor modulator
- Biphosphonates: Etdronate
- Sodium Fluoride: GI side effects
- Calcitonin: does not appear to benefit pts with cholestatic Osteoporosis.

2) Fat soluble vitamin Deficiency.
- Almost always caused by malabsorption resulting from the amount of bile salt in the intest lumen.
  + Vitam D: 50000 IU 1-2x week
  + Vitam A: 25-50000 IU 2-3x week
  + Vitam K: trial of 5-10 mg. If PT improves maintain on water soluble vitam K: 5mg/day.
- Vitam E: deficiency causes neurologic abnorm. Disappointing response to vitam E replacement.

PBC: COMPLICATIONS OF CHRONIC CHOLESTASIS AND MANAGEMENT.

3) Hypercholesterolemia and Hyperlipidemia.
- In 85% of pts with PBC
- Early disease: ↑ HDL
- Advanced disease: ↓ HDL and ↓ LDL
- Some pts: xanthelasmas 
- UDCA: ↓ LDL and useful in pts with xanthelasmas.

4) Pruritus.
- Pathogenesis is unknown.
  - Cholesthyramine: 3-12 g/day.
  - Rifampin: Benefit within a week: 150 mg BID
  - UDCA: can sometimes alleviate pruritus
  - Exposure to UVL without sun-block
  - Related to release of endogenous opioids: Nalmefene, Naltrexone (promising results).
  - Liver transplant: for severe intractable pruritus.
PBC: COMPLICATIONS OF CHRONIC CHOLESTASIS AND MANAGEMENT.
5) Steatorrhea.
- Substitution of M C trigl for long chain trigl and in total fat intake.
- Pancreatic replacement therapy
- Gluten withdrawal from diet
- Intermittent Abxs for bacterial overgrowth

PBC: LIVER TRANSPLANTATION.
- Best therapeutic alternative for end stage PBC
- Indications:
  - Poor quality of life due to disabling fatigue
  - Intractable pruritus
  - Major complications related to Portal HTN:
    + Bleeding for G-E varices
    + Diuretic resistant ascites
    + HRS
    + Hepatic encephalopathy
  - Persistent in bil in absence of hepatic malignancy

PBC: LIVER TRANSPLANTATION.
- Recent data: optimal survival in pts with Mayo risk score not exceeding 7.8(Kim,1998)
- 1 year survival rate after OLT: >90%
- 5 year survival rate: >80%
- Antimitochondrial Abs persist after OLT:10- 40% recurrence of PBC.
- 20% will need retransplant: Vanishing bile duct Sx
- Primary malignancies develop later in 10% of pts.

Autoimmune Variants
- AIH + PBC: 7%
- AIH + PSC: 6%
- AIH cholangitis: 11%

Steroids
- AIH + PBC: 75%
- AIH + PSC: 22%
- AIH cholangitis: 0%

Autoimmune Cholangitis or AMA-negative PBC
- Clinically, biochemically and histologically classic PBC
- AMA negative
- Most are ANA or ASMA positive
- Clinical course and treatment response to UDCA like AMA-positive PBC
- If bx suggests superimposed AIH UDCA + steroids

What to do…

Baseline Evaluation
- Imaging & Labs
- Assess symptoms
  - Pruritus
  - Fatigue
  - Sicca Syndrome
- Staging
- DEXA
- Initiate PBC-specific therapy
  - UDCA 13-15 mg/kg/day
- Long-term monitoring
  - Clinical evaluation
- Cirrhosis?
- MRS > 4.1?
- Thrombocytopenia
- EGD; HCC surveillance
- Biochemistries
- Risk stratification after 1 year of therapy
- Evaluate need for adjuvant therapy
- Transient elastography

HEPATOLOGY, August 1998, p. 360-365, Vol. 28, No. 2