Management of Cholestatic Liver Diseases

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MANAGEMENT OF PBC/PSC

• Epidemiology
• Natural history
• Diagnosis
• Symptoms
• Treatment
COMMON HEPATOBILIARY DISEASES ASSOCIATED WITH PRURITUS


MANAGEMENT OF PRURITUS

• Need to make correct diagnosis
  – Stones/Strictures/CA
  – PBC
  – PSC
  – IgG4
  – AIH
CHOLESTATIC LIVER DISEASES

• Definition
  – PBC
    • Alk phos > 2 x ULN
    • + AMA
    • Compatible liver biopsy
  – PSC
    • Cholangiogram abnormal
    • Compatible biopsy supportive

• Definition
  – AIH
    • ALT & AST > 5 x ULN
    • IgG > 2 x ULN
    • Periportal/interface hepatitis
MANAGEMENT OF PBC

• Medical Options:
  - Unsuccessful
    - penicillamine
    - cyclosporine
    - azathioprine
    - thalidomide
    - malotilate
    - chlorambucil
  - Questionable
    - steroids
    - colchicine
    - methotrexate
  - Useful
    - UDCA

TREATMENT OF PBC - URSODIOL

11 Randomized Trials
  – various sizes of study > 1200 patients
  – various doses
  – various endpoints
  – various duration (9 of 11 < 2 years)
NATURAL HISTORY OF PBC
Effects of UDCA

UDCA IN PBC

- Improves liver disease
- No consistent, reliable effect on pruritus

HIGH-DOSE URSO FOR PSC

RESULTS

Primary Endpoints

<table>
<thead>
<tr>
<th>Primary Endpoints</th>
<th>UDCA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Liver Transplant</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Minimal Listing Criteria for Liver Transplant</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Development of Cirrhosis</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Esophageal and/or Gastric Varices</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total Endpoints</td>
<td>52</td>
<td>29</td>
</tr>
</tbody>
</table>

Hepatology 2009;50(3):808-14
High-Dose UDCA for PSC

Incidence of Cholangiocarcinoma

Cumulative incidence of cholangiocarcinoma (%)

Years since PSC diagnosis
SURVIVAL FOR PSC PATIENTS WITH AND WITHOUT CCA

Lindor, personal communication

PRIMARY SCLEROSING CHOLANGITIS

Chronic cholestatic liver disease

- Unknown etiology
- Male:Female – 2:1, age group 40’s
- Frequently associated with IBD
- Diffuse inflammation, fibrosis, stricturing of biliary tree
- Progresses to biliary cirrhosis and portal hypertension
PRIMARY SCLEROSING CHOLANGITIS

DIAGNOSIS

- ERCP commonly used
- Magnetic resonance cholangiography emerging
  - non-invasive
  - no radiation

MRCP VS ERCP

- Similar diagnostic accuracy

Limitations of MRCP
- Lower sensitivity for subtle peripheral ductal abnormalities
- Subtle mural irregularities seen on ERCP maybe missed
- Does not permit therapeutic intervention
- Diagnosis or screening of cholangiocarcinoma not established
PRIMARY SCLEROSING CHOLANGITIS

MRCP image shows a high-grade hilar stricture (straight arrow) with proximal dilatation, multifocal intrahepatic strictures and dilatation, and a beaded appearance of the anterior right hepatic duct (curved arrow).


PRIMARY SCLEROSING CHOLANGITIS

Multifocal stricturing (thin arrows) and beading (thick arrows) of the intrahepatic and extrahepatic biliary ducts.
PRIMARY SCLEROSING CHOLANGITIS

Strictures can occur in any part of the biliary tree.

In one report of 100 patients, strictures found:

- Intrahepatic and extrahepatic bile ducts — 87%
- Intrahepatic bile ducts alone — 11%
- Extrahepatic bile ducts alone — 2%


PRIMARY SCLEROSING CHOLANGITIS

LIVER BIOPSY

- Rarely diagnostic; AASLD (2010) recommends against routine liver biopsy
- Helpful for staging and determining prognosis
- Diagnose small-duct PSC
- Suspect PSC-AIH
PRIMARY SCLEROSING CHOLANGITIS
PROGNOSTIC MODEL

Mayo PSC Risk Score Calculator

- Age, Total Bilirubin, Albumin, AST, Variceal bleed
- Score is ≤ 0 "low" risk group
- > 0 but < 2 "intermediate" risk group
- > 2 "high" risk group

- Each unit increase in Score - 2.5-fold increase in the risk of death
- Estimated probability of survival (%)

PRIMARY SCLEROSING CHOLANGITIS
HEPATOBILIARY MALIGNANCY

- 604 Swedish PSC patients; followed for 5.7 years
  - Hepatobiliary malignancy (CCA, HCC, GBC) - 13.3%
  - 161 fold increase risk of CCA
  - 10 fold increase risk of CRC

PRIMARY SCLEROSING CHOLANGITIS
CHOLANGIOCARCINOMA

- 10 to 15% lifetime risk
- 1.5% annual incidence
- Risk: Older age, alcohol, smoking, duration IBD, h/o CRC or dysplasia, variceal bleeding, proctocolectomy and polymorphisms of the NKG2D gene
- Duration of PSC not be a risk factor - half of malignancy is detected at the time of diagnosis or within the first year

Cholangiocarcinoma in a 29-year-old man with ulcerative colitis and primary sclerosing cholangitis who presented with jaundice and abdominal pain.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRCP</td>
<td>78</td>
<td>76</td>
</tr>
<tr>
<td>MRI/MRCP</td>
<td>89</td>
<td>75</td>
</tr>
<tr>
<td>MRI/MRCP+CA19-9</td>
<td>100</td>
<td>38</td>
</tr>
<tr>
<td>US + CA 19-9</td>
<td>91</td>
<td>62</td>
</tr>
</tbody>
</table>
PRIMARY SCLEROSING CHOLANGITIS
SCREENING FOR CCA

- Conventional cytology low sensitivity

- Fluorescence in situ hybridization (FISH)
  Positive FISH results - Sensitivity - 38%
  Specificity - 98%
  Accuracy - 83%

- ERCP complication - pancreatitis and cholangitis,

- ERCP with brushings for cytology and FISH analysis is a confirmatory test

PRIMARY SCLEROSING CHOLANGITIS
GALLBLADDER CANCER

- Prevalence 3-14% (vs 0.35% in general population)
- Male
- Younger age
- Risk factors – size >0.8cm
  - sessile
  - rapidly growing
  - presence of stones
  - older age

PRIMARY SCLEROSING CHOLANGITIS
HEPATOCELLULAR CARCINOMA

HCC incidence 1.5%

MRI or ultrasound

PRIMARY SCLEROSING CHOLANGITIS
COLORECTAL CARCINOMA

<table>
<thead>
<tr>
<th>UC DURATION</th>
<th>AT 10 YEARS</th>
<th>AT 20 YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC only</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>UC + PSC</td>
<td>9%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Risk factors: long duration
increased anatomic extent of colitis
More right sided lesions

PRIMARY SCLEROSING CHOLANGITIS

CRC SURVEILLANCE


PRIMARY SCLEROSING CHOLANGITIS

CRC CHEMOPREVENTION

- Urso maybe chemoprotective; however not recommended given the limited information available
- Folate supplementation
PRIMARY SCLEROSING CHOLANGITIS
UDCA

- 13-15 mg/kg
  - improvement in liver tests
  - no improvement in symptom or liver histology
  - no modification of primary outcomes (death, liver transplantation, cirrhosis, etc.)

- 20 mg/kg
  - improvement in biochemical and histology
  - long-term survival was not evaluated

- 17-23 mg/kg – trend towards increased survival

- 28-30 mg/kg – terminated prematurely

AASLD recommends against use of UDCA

Our protocol:
Stopping UDCA in patients already taking
Restart @13 to 15 mg/kg per day if:

- Bilirubin/ALT increases
- Worsening pruritus
- Patient preference
IgG4 ASSOCIATED CHOLANGITIS

IgG4-related disease is a systemic disease characterized by extensive IgG4-positive plasma cells and T-lymphocyte infiltration of various organs.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Name</th>
<th>Mimics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>Autoimmune Pancreatitis (AIP)</td>
<td>Pancreatic Cancer</td>
</tr>
<tr>
<td>Bile Ducts</td>
<td>IgG4-associated Cholangitis (IAC)</td>
<td>PSC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cholangiocarcinoma</td>
</tr>
</tbody>
</table>

IgG4 ASSOCIATED CHOLANGITIS
Differences Between PSC and IAC

<table>
<thead>
<tr>
<th></th>
<th>PSC</th>
<th>IAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>65%</td>
<td>80%</td>
</tr>
<tr>
<td>Age</td>
<td>25-45yr</td>
<td>65yr</td>
</tr>
<tr>
<td>IBD</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Advanced/end stage</td>
<td>Presenting sym 75%</td>
</tr>
<tr>
<td>Other organ invol</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>IgG4</td>
<td>9%</td>
<td>70%</td>
</tr>
<tr>
<td>Steroid</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>CCA</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
IgG4 ASSOCIATED CHOLANGITIS

**Serum IgG4 in IAC**
- 140 mg/dl: specificity 93%, sensitivity 76%, PPV 36%
- >280 mg/dl: specificity 99%, sensitivity 53%, PPV 75%

**IgG4 is not pathognomonic of IAC**
- 10% pancreatic cancer
- Pancreatitis
- 9% PSC
- 1% PBC

**Suspect IAC if:**
- Lower CBD stricture
- Segmental or long strictures with prestenotic dilatation
- Sclerosing changes intrahepatic and extrahepatic ducts
- Diffuse pancreatic involvement/pancreatic mass
IgG4 ASSOCIATED CHOLANGITIS

**Biliary Stricture**
- History
- Other organ invol.
- Cholangiogram

**Suspect IAC**

**Probable IAC**
- Elevated IgG4
- Endobiliary/Liver Biopsy

**Therapeutic Trial With Steroids**

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**IgG4 ASSOCIATED CHOLANGITIS**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IAC</strong></td>
<td>Bile duct wall thickening in a concentric pattern but luminal surface smooth</td>
</tr>
<tr>
<td><strong>CCA</strong></td>
<td>Abrupt and eccentric stricture with a irregular surface</td>
</tr>
<tr>
<td></td>
<td>Proximal biliary dilatation relatively mild</td>
</tr>
<tr>
<td></td>
<td>Marked proximal dilatation</td>
</tr>
<tr>
<td></td>
<td>Multifocal strictures with intervening normal-looking branches</td>
</tr>
<tr>
<td></td>
<td>Single localized stricture</td>
</tr>
</tbody>
</table>

AUTOIMMUNE PANCREATITIS/CHOLANGITIS IN PSC

- IgG4 elevated in 9% PSC patients
- These patients may be more steroid responsive.

NATURAL HISTORY “PSC” & IgG4

Am J Gastroenterol 2006;101:2070-75
PSC WITH ELEVATED IgG4—RESPONSE TO THERAPY

- 23 patients with PSC with elevated IgG4
- 5 patients with normal liver tests
- ~75% male; 75% with IBD
- ~50% with “dominant” strictures

18 treated with steroids

- Bili – 9/10 with elevated bili responded
  – 2.7 → 1.2
- Alk phos – 319 → 200 U/L at 2 months
- IgG4 – 285 → 125 mg/dL at 2 months
- Adverse steroid effects in 39%
- Relapse in 61%
PRIMARY SCLEROSING CHOLANGITIS
WHEN TO REFER FOR TRANSPLANT

Indications

- Similar to other causes
  - Hepatocellular

- Unique indications
  - intractable pruritus
  - recurrent bacterial cholangitis
  - Cholangiocarcinoma

- A Mayo model score of >5 or a Child C

PRIMARY SCLEROSING CHOLANGITIS
In A Nut Shell

- Chronic cholestatic liver disease
- Classic Cholangiogram
- Check IgG4 in all new patients with presumed PSC
- Mayo PSC Risk Score Calculator
- Screen for hepatobiliary carcinoma
- Urso is not recommended for treatment
- Refer patients early for consideration for liver transplant