Disclosure Slide

- Speakers Bureau: None
- Advisory board: Dova
- Grant Support: AbbVie
- This talk does contain off label use of drugs.
Overview

- Brief review of epidemiology, diagnosis, natural history, and treatment of
  - Primary biliary cholangitis (PBC)
  - Primary sclerosing cholangitis (PSC)
  - Immune-mediated hepatitis

- Abstracts and papers from 2018 chosen based on contribution to clinical practice
Primary Biliary Cholangitis

Autoimmune-mediated liver disease characterized by progressive small bile duct destruction and chronic cholestasis
PBC: Epidemiology

- Incidence has increased over time (70’-90’s)- better diagnosis or incident cases living longer (Gastro 2000:119;1631)
- Female to male ratio 9:1
- Median onset of disease is 50 yrs
- Associated conditions (Multiple rheumatological disorders, RTA, gallstones and thyroid disease)
- Risk Factors for PBC: familial, UTI, tobacco (Hepatology 2001:33;16)
PBC: Diagnosis

- Elevated AP with positive AMA: Hallmark of PBC; AMA=antibodies against PDC-E2; increased IgM
- Liver biopsy (mild proliferative changes around bile ducts with inflammatory cells spreading into lobules; florid duct lesion <10%)
  - If AMA+, AP > 1.5X ULN, AST < 5X ULN, PPV for PBC is 98% (*Clin Gastro and Hep 2003:1;89*)
  - Must biopsy if AMA – showing duct inflammation
  - AIH features (15-20%); Preductopenic features; staging of fibrosis
Large, prospective French study (n=229 follow-up 7 yrs)

Prevalence of AMA positive patients without evidence of PBC was 16.1 per 100,000.

More likely to be female with other AI diseases and lower titer AMA.

Among patients with normal ALP and no evidence of cirrhosis, the 5-year incidence rate of PBC was 16%.

EASL recommends annual LFT’s in these patients.
PBC: Diagnosis

Dense portal inflammation and poorly formed granuloma centered on bile duct
PBC: Diagnosis

Florid duct lesion – dense lymphocytic inflammation surrounding bile duct and infiltrating across the basement membrane into the biliary epithelium
PBC: Natural History

- UDCA decreases risk of cirrhosis and transplant
- Treating early stage PBC with UDCA results in mortality equal to that of general population (Gastro 2005:128;297)
- ANA+ is common
- 30% asymptomatic
- 10% with non-cirrhotic portal HTN
- Osteoporosis (about 30%)
- Pruritus, Fatigue, Sicca Syndrome common
Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases

Keith D. Lindor, Christopher L. Rosenthal, James Boyce, Cynthia Levy, and Marlyn Mayo

- Natural history, diagnosis, treatment
- Management of symptoms of PBC (pruritus, fatigue, sicca syndrome)
- Screening recommendations (osteoporosis, fat soluble vitamins, portal HTN, and HCC)
PBC: Treatment

- Ursodiol 13-15mg/kg/day- (>10 RCT’s)
- Prolonged treatment with UDCA, started at early stages of disease, is required to exert maximal positive effect
- Incomplete response in 30-40% (AP>1.67 X ULN)
- Liver Transplant (recurrence rate 25%)
Bile acids as enterohepatic hormones: Targets for PSC and PBC therapy

- Obeticholic acid (GS-9674)
- NGM282
- Seladelpar (PPARδ)
- Fibrates (PPARα)

Adapted from J of Hepatology 2015 62:S35-S61
POISE study: A Placebo controlled trial of Obeticholic Acid in PBC

- 5X more patients met primary endpoints in OCA arms than placebo
- Significant decrease in AP, AST, ALT, TB, ggt
- Decrease in inflammatory markers and serum bile acids and increase in FGF19
- No change in liver stiffness

Nevens et al NEJM 2016; 6;375:271
Obeticholic Acid in Patients with Decompensated Cirrhosis

FDA Officials Urge Proper Dosing of Liver Drug to Avoid Severe Damage

SEPTEMBER 21, 2017

Officials with the FDA issued a safety alert today warning that the liver disease medicine obeticholic acid (Ocaliva, Intercept Pharmaceuticals) is being incorrectly dosed, often in a higher frequency of dosing than recommended, in some patients with moderate to severe decreases in liver function, resulting in an increased risk of serious liver injury and death.

If OCA is initiated in a Childs B or C cirrhotic, the correct dosing is 5mg weekly (not daily) and may be titrated to 10mg twice weekly. These patients must be monitored.
OCA stabilized fibrosis in PBC patients after incomplete response to UDCA

- Histology sub-study of the POISE trial
- 13 patients with PBC who were incomplete responders to UDCA and started OCA
- Liver Biopsy at baseline and 3 years on therapy with OCA
- Of the 13 patients on OCA, histology improved in 6, maintained in 5 and worsened in 2. Of the 4 with cirrhosis, 3 had regression.
- This supports data that biochemical improvements seen in POISE trial with OCA will lead to improved clinical outcomes (Phase IV Cobalt study)

Bowlus et al LBP-014 EASL 2018
Phase 2 trial of 100 patients with an inadequate biochemical response to UDCA were randomized 1:1 to a 2-year treatment with either BZF 400 mg/d or placebo (PLB) in combination with UDCA 13-15 mg/kg/d.

In the BZF + UDCA group:
- 67% normalized AP
- 30% normalized all liver chemistries
- 75% improved itching score
- Improvements in liver stiffness and fibrosis markers
- 3 patients AST 5X ULN, 1 CK 5X ULN, 1 Cr bump

LB3: Efficacy and safety of Seladelpar, a selective PPAR-δ agonist, in patients with PBC: 52 week analysis of an international, randomized, dose ranging, phase 2 study

- 119 patients with inadequate response to UDCA (AP ≥ 1.67 ULN) or intolerance of UDCA were randomized

<table>
<thead>
<tr>
<th>Primary and secondary outcomes</th>
<th>5/10 mg (n=17)</th>
<th>10 mg (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seladelpar</td>
<td>Baseline Mean/Median AP</td>
<td>351/301 U/L</td>
</tr>
<tr>
<td>Responders* (n)</td>
<td>59% (10)</td>
<td>71% (12)</td>
</tr>
<tr>
<td>AP Mean Change</td>
<td>-47%</td>
<td>-46%</td>
</tr>
<tr>
<td>AP Normalized (n)</td>
<td>24% (4)</td>
<td>29% (5)</td>
</tr>
</tbody>
</table>

Seladelpar- % change AP from baseline and % of “Responders” in 5mg and 10mg groups

- Both the 5 and 10mg doses had significant anticholestatic effects; no pruritus from drug; well tolerated and no increased TA’s
- 52 wk global Phase III study ENHANCE ongoing

Bowlus et al LB-3AASLD 2018
AB 45: Liver stiffness does not change in 2 years in patients with PBC and incomplete response to UDCA

- 45 patients with PBC and incomplete response to UDCA (> 1.5X ULN) followed with liver stiffness measured by transient elastography (TE) and Magnetic Resonance Elastography (MRE) at baseline, 12, 24 mo
- Good concordance with TE and MRE readings with early F0-F2 or advanced F3-F4 fibrosis
- Liver stiffness was higher in those with AP> 1.5X ULN but did not change significantly over 2 yrs
Primary Sclerosing Cholangitis

Chronic cholestatic liver disease characterized by inflammation and fibrosis of biliary tree
PSC: Epidemiology

- Mean age at diagnosis is 40 with 2:1 male predominance
- Approximately 75% patients with PSC have IBD
- Cause unknown but immune and genetic mechanisms implicated
MRI/MRCP with contrast media should be the first diagnostic imaging modality in patients with suspected PSC.

Patients with suspected PSC should be assessed in experienced centers, which include the performance and interpretation of MRI.
PSC: Diagnosis

MRCP is primary diagnostic modality. ERCP if suspicion high and MRCP neg. Biopsy useful for diagnosing small duct PSC (5-10%) or overlap syndrome.
PSC: Natural History

- Progressive disease with “OLT free” survival of 12-17 years if symptomatic. *Mayo Clin Proc 2000:75;688*
- Leads to biliary cirrhosis and portal HTN
- Cholangiocarcinoma: Incidence 0.5-1%/year from diagnosis. *J Hepatol 2002:36;321*
- Colectomy does not alter PSC course. *(Scand J Gastro 2002:37;205)*
- PSC is an INDEPENDENT risk factor for colon cancer in IBD. *Hepatology 1995:22;1404*
Nationwide population-based evaluation of mortality and cancer-risk in young patients with UC/PSC.

In pts. diagnosed with UC age ≤40 years, development of PSC is associated with 6-fold increase in mortality and 7-fold increased risk of CRC when compared to UC alone.

Trivedi et al. Gut 2018;67:A103-A104
PSC: Treatment

- Ursodiol <20mg/kg/d may be of benefit
  \[(Gastro\ 2001;\ 121;\ 900)(AJG\ 2001;\ 96;\ 1558)(J.\ Hep\ 2008;\ 48;\ 792)\]

- Endoscopic stricture dilation and sphincterotomy

- Liver transplant (Recurrence 10-20%)
PSC: Ursodiol - more than metamucil for the bile ducts

- UDCA at <20 mg/kg/d
  - Improves biochemical abnormalities in PSC
  - No survival benefit or a delay in the need for liver transplantation
  - No prevention of strictures
  - Dose >25 mg/kg/d increase death and OLT rate
Is AP a reliable marker for risk of disease progression in PSC?

Survival free of PSC-related events according to AP tertiles

Levy et al J of Hepatology 2017 vol 66 S333-542
norUrsodeoxycholic acid Improves Cholestasis in PSC

- Side chain-shortened homologue of UDCA.
- In this phase II trial, norUDCA reduced serum ALP levels within 12 weeks.
- norUDCA’s effects on liver enzymes were dose-dependent.
- The safety profile of norUDCA was excellent.
- Currently in phase III trials in Europe.

Fickert et al J of Hepatol 2017 67(3)549
Antibiotic Therapy in PSC: Not quite ready for prime time...

<table>
<thead>
<tr>
<th>Drug</th>
<th>year</th>
<th>n</th>
<th>Antibiotic dose</th>
<th>Treatment duration</th>
<th>Change in ALP</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole + UDCA vs. placebo + UDCA</td>
<td>2004</td>
<td>80</td>
<td>600-800 mg/day</td>
<td>36 months</td>
<td>- 52%</td>
<td>50% on MTZ/UDCA had AEs</td>
</tr>
<tr>
<td>Minocycline</td>
<td>2009</td>
<td>16</td>
<td>200 mg/day</td>
<td>12 months</td>
<td>- 20%</td>
<td>25% discontinued due to AEs</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>2008</td>
<td>14</td>
<td>50 mg/kg (kids)</td>
<td>Up to 54 months</td>
<td></td>
<td>Normalization of GGT and ALT in non cirrhotics</td>
</tr>
<tr>
<td>Vancomycin vs. metronidazole</td>
<td>2013</td>
<td>18</td>
<td>Vanco: 125 or 250 mg qid</td>
<td>12 weeks</td>
<td>- 42%</td>
<td>6 patients discontinued study due to AE, 4 in MTZ group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17</td>
<td>MTZ: 250 or 500 mg tid</td>
<td></td>
<td>- 10%</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>2016</td>
<td>29</td>
<td>125 mg qid</td>
<td>12 weeks</td>
<td>- 45%</td>
<td></td>
</tr>
<tr>
<td>Rifaximin</td>
<td>2017</td>
<td>16</td>
<td>550 mg bid</td>
<td>12 weeks</td>
<td>No change</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from C Levy AASLD Post Grad Course 2017
AB 43: The non-steroidal FXR agonist GS-9674 improves liver biochemistry and decreases serum bile acids in PSC

Double blind, randomized, placebo controlled trial of 2 doses of GS-9674 for 12 weeks in 52 patients with large duct PSC and AP $\geq$ 1.67 ULN
AB 43: The non-steroidal FXR agonist GS-9674 improves liver biochemistry and decreases serum bile acids in PSC

- GS-9674 resulted in:
  - Decrease in AP regardless of UDCA use
  - Reduction in ggt, ALT, C4, TIMP-1, and serum bile acids
  - Decrease in grade 2-3 pruritus - 100mg (14%), 30mg (20%) and placebo (40%)

Trauner et al. AB43 AASLD 2018
NGM282, an engineered analogue of FGF19, improves markers of bile acid synthesis, hepatic injury and fibrosis in PSC.

- Fibroblast growth factor (FGF) 19 is a hormone which acts in the liver to regulate bile acid synthesis.
- Significant dysregulation of FGF19 in PSC

Hirschfield et al. LBO-022 EASL 2018
NGM282, an engineered analogue of FGF19, improves markers of bile acid synthesis, hepatic injury and fibrosis in PSC.

- In pre-clinical studies with NGM282, significant decrease in hepatobiliary fibrosis in Mdr2-/- mouse model of PSC

Zhou et al Hepatology 2016
NGM282, an engineered analogue of FGF19, improves markers of bile acid synthesis, hepatic injury and fibrosis in PSC.

- Double blind, randomized, placebo controlled trial of 2 doses of SQ NGM282 for 12 weeks in 62 patients with large duct PSC and AP ≥ 1.5 ULN, AST/ALT < 5X ULN, TB < 2.5
- NGM282 did not show sustained decrease in AP levels but did show significant drops in anti-fibrotic and anti-inflammatory activity via reduction in C4, bile acids, AST, ALT, PRO-C3 and ELF score.

NGM282 rapidly suppresses PRO-C3 supporting suppression of fibrogenesis
Statins associated with lower risk of liver transplant and death in PSC

- Retrospective cohort study evaluating 2914 Swedish patients with PSC and dx of UC or Crohns
- About 14% received statins (404)
- There was a 32% decreased risk in all cause mortality and a 50% decreased risk of liver related mortality, liver TP, and adverse liver events.
- Hypothesis generating study showing that statins are a promising candidate for future clinical trials in PSC
Vedolizumab (VDZ) blocks gut homing lymphocytes so an attractive target in PSC patients with IBD.

- Retrospective review of 60 patients with PSC/IBD by the International PSC Study Group.
- Median duration of VDZ was 363 days (range 14–2609) with 28 patients (46.7%) stopping during study most due to lack of efficacy (21, 75%).
- VDZ appeared moderately effective for IBD in PSC/IBD, but with no effect on AP response, (trend towards AP rise), and a small rise in ALT, likely due to the natural course of the underlying PSC.
Did you know...

PSC did not have it’s own ICD 10 code until October 2018?

K83.01
PRO’s in PSC

Welcome to the PSC Partners Patient Registry

Help researchers worldwide unlock the mysteries of primary sclerosing cholangitis (PSC). Complete your profile and join PSC Partners Seeking a Cure in advancing PSC research towards a cure. Your participation is important!

The PSC Partners Patient Registry was established in collaboration with the National Institutes of Health (NIH) The Office of Rare Diseases Research.

Join the Registry!
PSC Registry Instructions

pscpartners.org
Why have PROs become so popular?

Health outcomes other than Length of Survival and Drug Efficacy matter to patients.

Survival or Physiological Endpoints ≠ Better Quality of Life
Who cares about PROs?

Multiple agencies….

The “Regulators”
FDA

The “Payers”
Center for Medicare and Medicaid

The “Funders”
NIH
PCORI
Immune-related acute hepatitis of all grades is estimated to affect 4% and 9% of patients treated with anti-CTLA-4 mAbs, and 18% of patients treated with the combination of anti-PD-1 and anti-CTLA-4 mAbs with anti-PD-1 alone lower at 1-4%.
Blocking T cell downregulation
Characterization of liver injury due to immune checkpoint inhibitor cancer therapy

AI-like diseases when block T cell inhibition

Ipilimumab

Pembrolizumab
Nivolumab
Durvalumab

Based on biological and histological severity of liver injury
Surveillance or corticosteroid therapy

De Martin et al J Hepatol Oct 2018 vol 68: 1181
Incidence of grade 3 or 4 liver injury with immune checkpoint inhibitors - Retrospective

Grade 3-4 liver injury corresponded to an increase of more than five times the upper limit of normal range in any liver function test (AST, ALT, AP, ggt)

Parlati et al J Hepatol 2018 vol 69: 1396
Characterization of liver injury due to immune checkpoint inhibitor cancer therapy

- Management based on clinical course and histologic features
- Hepatitis occurred median 14 wks with anti-PD1 vs median 4 wks with anti-CTLA4 alone or in combination
  - Serum auto-Abs usually low titer or negative
  - 6 patients did not get steroids (38%)

De Martin et al J Hepatol Oct 2018 vol 68: 1181
Characterization of liver injury due to immune checkpoint inhibitor cancer therapy

Anti-CTLA4: can show granulomatous hepatitis

Anti-CTLA4: endothelialitis with CD8+ T cells

Anti-PD-1: mild portal and interface hepatitis with lymphocytic infiltrates (mixed CD4 and CD8 T cells)
Histologic characteristics of patients with immune-mediated hepatitis

All patients treated with corticosteroids 1 mg/kg showed more severe histological damage compared with patients not treated; specifically grade 3 inflammation in at least one zone and central endotheliitis.

De Martin et al J Hepatol Oct 2018 vol 68: 1181
Management of grade 3 liver injury or higher from anti-PD1 inhibitor

<table>
<thead>
<tr>
<th>Condition</th>
<th>AST or ALT more than 3 and up to 5 times the upper limit of normal (ULN) or total bilirubin more than 1.5 and up to 3 times the ULN</th>
<th>Withhold dose</th>
<th>Permanently discontinue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis HCC</td>
<td>AST or ALT more than 5 times the ULN or total bilirubin more than 3 times the ULN</td>
<td>Permanently discontinue</td>
<td></td>
</tr>
</tbody>
</table>
Algorithm for the assessment and management of patients with acute hepatitis during immunotherapy for metastatic cancer.

- While the incidence may be increasing, diagnosis needs to be accurate so biopsy is essential.
- May also show additional underlying liver disease skewing severity.
- Not ALL patients require steroids.

De Martin et al J Hepatol Oct 2018 vol 68: 1181