Hepatobiliary manifestations of Inflammatory Bowel Disease

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University of Toronto PSC-IBD Programme

Toronto, November 2018
## Disclosure of Conflict of Interest

I have a relationship with a for-profit and/or a not-for-profit organization to disclose:

<table>
<thead>
<tr>
<th>Nature of relationship(s)</th>
<th>Name of for-profit or not-for-profit organization(s)</th>
<th>Description of relationship(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any direct financial payments including receipt of honoraria</td>
<td>Intercept, Cymabay, GSK, Novartis</td>
<td>Scientific consultancy in the development of new drugs for patients with PBC</td>
</tr>
<tr>
<td>Membership on advisory boards or speakers’ bureaus</td>
<td>Intercept, Falk</td>
<td>I have presented my own slides at CME meetings with Industry sponsorship</td>
</tr>
<tr>
<td>Funded grants or clinical trials</td>
<td>Gilead</td>
<td>Educational grant to support operating costs of UK-PSC, a national observational study</td>
</tr>
<tr>
<td>Patents on a drug, product or device</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity</td>
<td>Intercept, Gilead, Novartis, GSK, Falk, NGM Bio, Cymabay</td>
<td>I have been the local study investigator of early stage industry sponsored clinical trials in patients with PBC and PSC.</td>
</tr>
<tr>
<td>X</td>
<td>Medical Expert</td>
<td>Communicator</td>
</tr>
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<td></td>
<td>(As Medical Experts, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centred care. Medical Expert is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)</td>
<td>(As Communicators, physicians form relationships with patients and their families* that facilitate the gathering and sharing of essential information for effective health care)</td>
</tr>
</tbody>
</table>
At the end of this session, the participant will be able:

1. To understand the breadth of hepatobiliary concerns seen in patients with IBD
2. To appreciate the approaches to effective diagnosis and current management
3. To recognize why PSC-IBD is a distinct entity necessitating development of a separate care pathway
4. To be conversant in the latest trial opportunities for patients
Overview

**Related or Associated**

- Medication side effects
  - Azathioprine
  - Methotrexate
  - Biologics
  - 5-ASA

- Disease Association
  - Sclerosing cholangitis
  - Autoimmune hepatitis
  - Portal vein thrombosis/Budd-Chiari
  - Nodular regenerative hyperplasia

**Unrelated but relevant**

- Independent liver disease
  - Hepatitis B and immunosuppression
  - Hepatitis E
  - Cirrhosis and portal hypertension
  - NAFLD
Risk factors for liver injury are not rare

- Age/Renal function
- Alcohol
- Obesity
- Diabetes
- Pre-existing liver disease
- Concomitant medications e.g. Methotrexate, Azathioprine, anti-TNF
Non-invasive markers of fibrosis

• Alternatives to liver biopsy are attractive, not just to the Hepatologist
  
  – Serum markers

  – Transient elastography
    • BUT it is just a number; beware the report that implies it is something it isn’t!
    • Never use it as an absolute classifier of fibrosis or steatosis
    • use it as an **ADJUNCT** to your care plan
# PSC-IBD Programme: A challenge and an opportunity

## Synopses
- Fluctuating colitis/Early PSC
- Active IBD on Vedolizumab in patient with cirrhosis and portal hypertension (Fibroscan >50kPa)
- Recurrent cholangitis secondary to stricturing PSC (rotating antibiotics)
- New presentation of PSC-IBD (hepatitic with colitis)
- PSC on transplant waiting list
- Advanced cirrhotic PSC in patient initially with ASC/IBD
- Progressive biliary changes on MRI (normal LFTs)
- Asymptomatic PSC with ALP >2.5xULN
- Symptomatic PSC with colitis ?up titrate to biologic
- Dukes C CRC post-OLT
- Symptomatic recurrent PSC in liver graft(s)

## Demographics
- All ages; whole families
- Men and women
- Pan-ethnicity
- From mild to end-stage disease
- Pre- and post- transplant
- Benign and malignant disease
- Co-existent extra-hepatic manifestations
Sclerosing cholangitis - one black box in GI Medicine

Chronic bile duct disease leading to fibrotic strictures and saccular dilatations of the intra- and extrahepatic bile ducts
Ulcerative C(h)ol(ang)itis

How many new patients get disease each year?

- PBC – 2.3 (2.2-2.4) \(\text{cf.} 0.3-5.8\)
- PSC – 0.7 (0.6-0.7) \(\text{cf.} 0-1.3\)
- AIH – 1.7 (1.6-1.8) \(\text{cf.} 1.68 (1.60\text{ to }1.76)\) Denmark
  - cases/100,000/year from 1998-2015
- \(\text{cf.} \) Multiple Sclerosis – 5.5 (5.1-5.9) and T2DM – 396 (394-398)

Patchy disease characterised by strictures, inflammation and malignancy risk

IPSCSG Clinical cohort

Weismueller, Trivedi et al. Gastro 2017
FIG. 1. (A) Development of portal hypertensive complications after diagnosis of PSC. (B) Survival with native liver after diagnosis of portal hypertensive complications. (C) Development of biliary complications after diagnosis of PSC. (D) Survival with native liver after diagnosis of biliary complications. (E) Survival with native liver. (F) Event-free survival.
In particular, the strong comorbidity between primary sclerosing cholangitis and inflammatory bowel disease is likely the result of a unique disease, which is genetically distinct from classical inflammatory bowel disease phenotypes.
Immunity/Inflammation

Cholestasis

Fibrosis
Evaluation

Cholestatic liver biochemistry

Adequate exclusion of other liver diseases and secondary sclerosing cholangitis, including IgG4-associated sclerosing cholangitis
Normal liver biochemistry does not preclude a diagnosis

Imaging

MRI-based cholangiography for diagnosis
Endoscopic cholangiography generally reserved for intervention

Liver biopsy

If normal cholangiography (small-duct primary sclerosing cholangitis)
If concurrent autoimmune hepatitis (overlap) is suspected

Colonoscopy

Full colonoscopy with biopsies is recommended if no known inflammatory bowel disease
When inflammatory bowel disease is present, screening for dysplasia usually every year

High dose UDCA vs. Placebo

Model of All Primary Endpoints
Adjusted for Mayo Risk Score, Presence of Varices, and Stage

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Time to Event (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDCA</td>
<td>76 73 60 51 34 18 9 0</td>
</tr>
<tr>
<td>PLACEBO</td>
<td>74 65 60 58 41 24 7 0</td>
</tr>
</tbody>
</table>

$p = 0.008$
Tipping point: stage and risk are different

Changes in LSM as estimated by the linear mixed model

(A) as a function of time and initial stage of fibrosis

(B) as a single continuous process extrapolated from the means of progression rates.

Corpechot et al. Gastroenterology 2014
Stratification

• Stage (Fibroscan, ELF, MRI, Biopsy)

• Severity and risk (Liver biochemistry)

• Treatment (UDCA)
PSC-IBD has the 3C(onfounder)s

- **Cholangitis**: ALP goes up and down and up and down
  - key difference between ALP in PSC and PBC
- **Cholangiocarcinoma**: patient dies but therapy effective?

- **Colitis**: quality of life declines at same time as liver settles; colitis activity and non-invasive markers of liver fibrosis
  - How do you stratify for IBD in recruitment?
New Therapeutic Opportunities

**Bile Acids**
- FXR/FGF19 axis?
- Microbiome manipulation?
- PPARs?
- Bile acid uptake inhibition?
- Augment HCO$_3^-$ secretion?

**BEC Injury and its response**
Down-regulation of AE2 sensitizes cholangiocytes to apoptotic insults

**Immunoregulation**
- Secretome inhibitors?
- Immunomodulation/Cell therapy?
- Cell recruitment & adhesion?

**Fibrosis**
- Epithelial protectants?
- Anti-fibrotics?

**New Therapeutic Opportunities**
- Augment HCO$_3^-$ secretion?
- PPARs?
- Down-regulation of AE2 sensitizes cholangiocytes to apoptotic insults
norUDCA Phase 2 Trauner et al. Relative Changes in ALP From Baseline to EOT (ITT)

Values (%) are means (SD)

Slide courtesy of Prof Trauner/Falk
ILC 2016
The AESOP Trial (Kowdley et al 2017):
A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of Obeticholic Acid in Patients with Primary Sclerosing Cholangitis
The ADAMS hypothesis

Gut homing lymphocytes

Endothelial cell

PSC Liver infiltrating lymphocytes

 Courtesy of Prof. D Adams
Williamson et al. IPSCSG Vedo study

Change in ALP (x ULN*)

<table>
<thead>
<tr>
<th>Timepoint on VDZ</th>
<th>ALPxULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Mean 2.02</td>
</tr>
<tr>
<td>Day 42</td>
<td>Mean 2.25</td>
</tr>
<tr>
<td>Day 98</td>
<td>Mean 2.38</td>
</tr>
<tr>
<td>Last f/u</td>
<td>Mean 2.55</td>
</tr>
</tbody>
</table>

Change in ALT

<table>
<thead>
<tr>
<th>Timepoint on VDZ</th>
<th>ALT (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Mean 57.7</td>
</tr>
<tr>
<td>Day 42</td>
<td>Mean 71.3</td>
</tr>
<tr>
<td>Day 98</td>
<td>Mean 78.5</td>
</tr>
<tr>
<td>Last f/u</td>
<td>Mean 78.2</td>
</tr>
</tbody>
</table>

Change in bilirubin

<table>
<thead>
<tr>
<th>Timepoint on VDZ</th>
<th>Bilirubin (umol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Mean 16.3</td>
</tr>
<tr>
<td>Day 42</td>
<td>Mean 17.2</td>
</tr>
<tr>
<td>Day 98</td>
<td>Mean 17.5</td>
</tr>
<tr>
<td>Last f/u</td>
<td>Mean 29.5</td>
</tr>
</tbody>
</table>

Wilcoxon analyses

Mean +/- SD shown on graphs

*ULN = upper limit of normal

^if ALP ULN=220

ns p > 0.05
* p ≤0.05
** p ≤0.01
***p ≤0.001
Efficacy and safety of simtuzumab for the treatment of primary sclerosing cholangitis: results of a phase 2b, dose-ranging, randomized, placebo-controlled trial

<table>
<thead>
<tr>
<th>Endpoints at Week 96</th>
<th>SIM 75 mg (N = 79)</th>
<th>SIM 125 mg (N = 77)</th>
<th>Placebo (N = 78)</th>
<th>P-value 75 mg vs. placebo</th>
<th>P-value 125 mg vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change in hepatic collagen,¹ %</strong> Mean (SD)</td>
<td>−0.5 (5.78)</td>
<td>0.5 (6.94)</td>
<td>0.0 (4.76)</td>
<td>0.73</td>
<td>0.33</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>−0.6 (−3.3, 0.7)</td>
<td>−1.1 (−2.8, 1.6)</td>
<td>−0.9 (−2.3, 0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ishak Fibrosis Stage,² % (n)</strong> Worsening</td>
<td>33.8 (26)</td>
<td>32.8 (22)</td>
<td>44.4 (32)</td>
<td>0.12</td>
<td>0.13</td>
</tr>
<tr>
<td>Improvement</td>
<td>32.5 (25)</td>
<td>31.3 (21)</td>
<td>22.2 (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Events,³ % (n)</strong> All</td>
<td>20.3 (16)</td>
<td>18.2 (14)</td>
<td>17.9 (14)</td>
<td>0.74</td>
<td>0.84</td>
</tr>
<tr>
<td>Ascending cholangitis</td>
<td>15.2 (12)</td>
<td>14.3 (11)</td>
<td>9.0 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Change in ALP,⁴ U/L</strong> Mean (SD)</td>
<td>−30 (116.0)</td>
<td>−2 (128.6)</td>
<td>−4 (155.5)</td>
<td>0.29</td>
<td>0.94</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>−12 (−98, 16)</td>
<td>−7 (−50, 38)</td>
<td>4 (−25, 42)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Muir et al. 2017
NGM282 (FGF19 analogue): No Sustained Changes in ALP, GGT or Total Bilirubin

UDCA use did not impact treatment response at W12

Hirschfield et al. In Press
NGM282 Decrease Liver Transaminases Supporting an Improvement in Hepatic Inflammation

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Absolute D at W12</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-4.5 (31.6)</td>
<td>0.255</td>
<td></td>
</tr>
<tr>
<td>NGM282 1mg</td>
<td>-2.8 (62.8)</td>
<td>0.409</td>
<td></td>
</tr>
<tr>
<td>NGM282 3mg</td>
<td>-42.7 (74.5)</td>
<td>&lt; 0.001</td>
<td></td>
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<table>
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<th>Mean (SD)</th>
<th>Absolute D at W12</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-5.3 (25.6)</td>
<td>0.068</td>
<td></td>
</tr>
<tr>
<td>NGM282 1mg</td>
<td>-11.2 (62.2)</td>
<td>0.974</td>
<td></td>
</tr>
<tr>
<td>NGM282 3mg</td>
<td>-24.5 (50.2)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

Hirschfield et al. In Press
NGM282 Rapidly Decreases PRO-C3 Levels Supporting a Suppression of Fibrogenesis

![Graph showing PRO-C3 levels across study weeks for Placebo, 1 mg, and 3 mg treatment groups.](image)

Hirschfield et al. In Press
The microbiota is different in patients with PSC-IBD

- Significant difference in the composition of the microbiota between conditions, irrespective of biopsy site ($p=0.001$).
- This was confirmed by constrained ordination, which resulted in clear separation between the three groups.

Qureshi et al. Gut 2016
Vancomycin or metronidazole in patients with primary sclerosing cholangitis

VANCOMYCIN

METRONIDAZOLE

Alimentary Pharmacology & Therapeutics 2013, pages 604-612, 5 FEB 2013 DOI: 10.1111/apt.12232
<table>
<thead>
<tr>
<th>Treatment Theme</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ursodeoxycholic acid treatment</td>
<td>No clear survival benefit; risk of harm with doses of 28–30 mg/kg per day</td>
</tr>
<tr>
<td>Ursodeoxycholic acid chemoprevention</td>
<td>Decreased risk of colon cancer and cholangiocarcinoma not shown</td>
</tr>
<tr>
<td>Disease with features of autoimmune hepatitis</td>
<td>Histologically proven autoimmune hepatitis should be treated as such; intervention for serological overlap discouraged; disease onset at younger age is more frequently hepatic in nature and more frequently has overlapping features; overlap does not represent a distinct disease</td>
</tr>
<tr>
<td>IgG4-associated disease</td>
<td>Routine measurement of IgG4 concentrations and imaging of pancreas essential; intervention recommended for overt disease; slight increases in IgG4 concentrations are common and potentially stratifying, but intervention with steroids unproven</td>
</tr>
<tr>
<td>Pruritus and fatigue</td>
<td>Common; concerns about quality of life important</td>
</tr>
</tbody>
</table>

Table 2: Treatment themes in primary sclerosing cholangitis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biliary intervention</strong></td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis during endoscopic retrograde cholangiography</td>
<td>Absolute necessity (eg, ciprofloxacin)</td>
</tr>
<tr>
<td>Long-term antibiotics</td>
<td>Unproven; consider in recurrent cholangitis; consider rotating antibiotics (eg, amoxicillin-clavulanic acid, ciprofloxacin, co-trimoxazole)</td>
</tr>
<tr>
<td>Endoscopic treatment</td>
<td>Centre-specific practice; risk of biliary sepsis (concurrent and future) vs benefit of early diagnosis of malignancy; intervention for dominant biliary strictures</td>
</tr>
<tr>
<td><strong>Transplantation</strong></td>
<td></td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>Established indications include decompensated cirrhosis (UK model for end-stage liver disease score ≥49), intractable cholangitis, biliary obstruction, hepatocellular carcinoma; debated indications include biliary dysplasia, hilar cholangiocarcinoma, pruritus</td>
</tr>
<tr>
<td><strong>Surveillance</strong></td>
<td></td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Increased risk of colon cancer in patients with concomitant inflammatory bowel disease necessitates annual colonoscopy with screening biopsies</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>Annual imaging of gallbladder; six monthly surveillance for hepatocellular carcinoma once patient is cirrhotic</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>Consensus not reached; challenges with performance characteristics of carbohydrate antigen 19-9 and cytology in particular</td>
</tr>
<tr>
<td>Bone density</td>
<td>Increased prevalence of low bone mass; consider estimation of overall fracture risk</td>
</tr>
<tr>
<td>Family</td>
<td>Not recommended (familial disease is rare)</td>
</tr>
</tbody>
</table>

*Table 1: Issues in management of primary sclerosing cholangitis*

Beyond the liver

- Fatigue
- Pruritus
- Concurrent autoimmune diseases
- Reduced bone density
- Abdominal pain
- Complications of IBD/Pouch

PSC can range from asymptomatic and slowly progressive to symptomatic and rapidly evolving.

Adapted from original slide of Kris Kowdley
University of Toronto PSC-IBD Programme

Monitoring
- Patient reported outcomes
- Timing of transplantation
- Cancer risk

Symptoms
- Complications
- Co-morbid disease

Physical illness

Social isolation
- Perception of being a burden
- Stigmatisation
- Rare disease

Perception

Fear & Uncertainty
- Unpredictable progression
- Economic consequences
- No effective treatment

Research
- Clinical trials
- Risk stratification
- Surrogate end-points

Understanding
- Communication
- Information
- Support

Quality of Care
- Access
- Expertise
- Consistency

Hepatology 2018