Autoimmune and cholestatic liver diseases

Prof. Tom Hemming Karlsen
Research Institute of Internal Medicine &
Department of Transplantation Medicine
University of Oslo & Oslo University Hospital, Norway

Johannesburg 24th of November 2018
A changing landscape of liver research

(Karlsen and Tacke, 2018)
How to accomplish HBV cure?

(Lok et al., 2017)
The race for new NAFLD drugs to market

(Konermann et al., 2017)
The race for new NAFLD drugs to market

(Konermann et al., 2017)
Liver oncology and new drugs in HCC
So what about autoimmune and cholestatic?
Primary biliary cholangitis
Ursodeoxycholic acid in PBC

- Barcelona (ALP 40% decrease or normalization) – 39%
- Paris (ALP <3ULN, AST <2ULN, bilirubin <1mg/dl) – 39%
- Rotterdam (bilirubin and albumin normalization) – 24%
- Toronto (ALP <1.67ULN and/or bilirubin <1mg/dl) – 43%
- Mayo (ALP <2ULN or bilirubin 1mg/dl) – 52%

- New algorithms occurring regularly
UDCA without biochemical improvement?

Reduction after 1-year UDCA  No reduction after 1-year UDCA  No treatment

Alkaline phosphatase

Bilirubin

Adj. HR 0.61 (IQR 0.46–0.81)
P<0.001 for all comparisons

Adj. HR 0.55 (IQR 0.45–0.67)
P<0.001 for all comparisons

Harms et al., EASL 2018
OCA – phase II and phase III studies

A

Percent change in ALP

B

Percent patients

Transition to open-label phase

Hirschfield et al., 2015
Nevens et al., 2016
Pruritus and obeticholic acid

Hirschfield et al., 2015
Nevens et al., 2016
OCA in cirrhosis – FDA (September 2017)

FDA Drug Safety Communication: FDA warns about serious liver injury with Ocaliva (obeticholic acid) for rare chronic liver disease

[9-21-2017] The Food and Drug Administration (FDA) is warning that the liver disease medicine Ocaliva (obeticholic acid) is being incorrectly dosed in some patients with moderate to severe decreases in liver function, resulting in an increased risk of serious liver injury and death. These patients are receiving excessive dosing, particularly a higher frequency of dosing than is recommended in the drug label for them. Ocaliva may also be associated with liver injury in some patients with mild disease who are receiving the correct dose. The recommended dosing and monitoring for patients on Ocaliva are described in the current drug label. We are working with the drug manufacturer, Intercept Pharmaceuticals, to address these safety concerns.

Ocaliva is used to treat a rare, chronic liver disease known as primary biliary cholangitis (PBC). PBC causes the bile ducts in the liver to become inflamed, damaged and destroyed. This causes bile, a fluid that helps in digestion, to build up in the liver. This build-up damages the liver over time, eventually causing it to lose its ability to function. Ocaliva has been shown to improve a certain blood test that measures liver problems.

Health care professionals should determine the patient's baseline liver function prior to starting Ocaliva. Patients with moderate to severe liver impairment (Child-Pugh B and C) should be started on the approved dosing schedule of 5 mg once weekly, rather than the 5 mg daily dosing used for other PBC patients, and if needed, can be increased up to a maximum approved dose of 10 mg twice weekly. Health care professionals should monitor patients frequently for disease progression, and reduce the dosing frequency to once- or twice-weekly for patients who progress to moderate or severe liver impairment. In all patients treated with Ocaliva, monitor frequently for liver injury (e.g., worsened liver blood tests and adverse liver-related reactions that may be inconsistent with the patient’s extent of disease). If liver injury is suspected, discontinue Ocaliva. After the patient has stabilized, weigh the benefits against the risks when deciding whether to re-initiate treatment. Educate patients on the symptoms of potential liver injury.

Patients should contact their health care professional if they have questions or concerns about taking Ocaliva. Report new or worsening severe skin itching to your health care professional. Also contact them immediately if you develop any of the following symptoms that may be signs of liver injury.
<table>
<thead>
<tr>
<th>Staging/Classification</th>
<th>Non-Cirrhotic or Child-Pugh Class A</th>
<th>Child-Pugh Class B or C or Decompensated Cirrhotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting Dosage</strong></td>
<td>5 mg once daily</td>
<td>5 mg once weekly</td>
</tr>
<tr>
<td><strong>Dosage Titration</strong></td>
<td>For patients who have not achieved an adequate reduction in alkaline phosphatase (ALP) and/or total bilirubin after 6 months of treatment and the patient is tolerating obeticholic acid, titrate up to 10 mg once daily.</td>
<td>For patients who have not achieved an adequate reduction in ALP and/or total bilirubin after 3 months of treatment and the patient is tolerating obeticholic acid, titrate up to 5 mg twice weekly (at least 3 days apart) and subsequently to 10 mg twice weekly (at least 3 days apart) based on response and tolerability.</td>
</tr>
<tr>
<td><strong>Maximum Dosage</strong></td>
<td>10 mg once daily</td>
<td>10 mg twice weekly (at least 3 days apart)</td>
</tr>
</tbody>
</table>
Tropifexor – non-bile acid FXR agonist

**Absolute GGT**

**Absolute ALT**

*\( p < 0.05 \); †\( p < 0.01 \); ‡\( p < 0.001 \) vs. placebo

Schramm et al., EASL 2018
Bezafibrate (pan-PPAR agonist)

Corpechot et al., NEJM 2018
## Bezafibrate (pan-PPAR agonist)

### Table 3. Incidence of Adverse Events Occurring in 10% or More of Patients and All Serious Adverse Events.

<table>
<thead>
<tr>
<th>Event</th>
<th>Bezafibrate Group (N = 50)</th>
<th>Placebo Group (N = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>43 (86)</td>
<td>45 (90)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 (14)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>10 (20)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9 (18)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4 (8)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Depressive mood</td>
<td>7 (14)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7 (14)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (8)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Flulike syndrome</td>
<td>5 (10)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>14 (28)</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Aminotransferase level &gt;5x ULN</td>
<td>3 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Creatine kinase level &gt;5x ULN</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine increase with worsening stage of chronic kidney disease</td>
<td>1 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>
Seladelpar (selective PPARδ agonist)

Jones et al., 2017
Seladelpar (selective PPARδ agonist)

5 mg n = 12 (except for Month 3, n = 11)
10 mg n = 11
LS Mean ± SE
LS = Least Squares
No statistical differences between dose groups

<table>
<thead>
<tr>
<th>Seladelpar</th>
<th>5/10 mg (n=17)</th>
<th>10 mg (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Mean/Median AP</td>
<td>351/301 U/L</td>
<td>279/248 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>

*AP < 1.67 x ULN, ≥15% decrease in AP, and total bilirubin ≤ ULN.

Hirschfield et al., AASLD 2017
Hirschfield et al., AASLD 2018
Budesonide (GR and PXR agonist)

Improved liver histology†

Improved liver function

<table>
<thead>
<tr>
<th>Mean change from baseline (SD)</th>
<th>Placebo (n=40)</th>
<th>BUD (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (U/L)</td>
<td>−0.16 (46.8)</td>
<td>−12.1 (30.2)</td>
</tr>
<tr>
<td>AP (U/L)</td>
<td>−8.9 (176.94)</td>
<td>−94.5 (166.3)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.59 (2.2)</td>
<td>−0.02 (0.4)</td>
</tr>
</tbody>
</table>

(Hirschfield et al., EASL 2018)
Symptoms management in PBC

Primary biliary cholangitis (PBC)
Living with your diagnosis

The PBC Network

Managing your symptoms

It is possible to have PBC without knowing, but many people experience a number of symptoms, which may appear at any time and can affect your daily life.

Symptoms of PBC include:
- Itching
- Tiredness
- Dry mouth, eyes, and intimate areas (vocal cords)
- Joint pain
- Stomach ache
- Restless legs.

Treatment for your PBC will not alleviate your symptoms, but these can often be treated and improved if the right guidance is followed. Not all clinics and doctors will have expertise in treating PBC symptoms; this guide offers you advice on how best to manage them.

Please ask your doctor for advice if you experience any symptoms, or if your symptoms change. They may give you a questionnaire to fill in, to get a full picture of how PBC impacts your life.

How to deal with itching
Itching is a common symptom of PBC, although not all patients will have it. Indeed, some people may find that their itching improves while their condition worsens. Itching due to PBC can often be treated and improved, but there is no one-size-fits-all treatment. Instead, your doctor should look at your individual situation.

Your itching could be due to cholestasis, where the bile ducts in your liver are blocked. This could happen due to gallstones, or other complications from your condition. Itching may be especially strong if you have a form of PBC called ‘ductopenic variant’, where the bile ducts in your liver have disappeared.

There are medications available to help, but they may not be suitable or effective for everyone. Sometimes, a few practical measures can bring relief.

- Emollients and oatmeal extract can soothe dry and inflamed skin.
- Cold baths or showers may help, especially if your itching is triggered by heat.
- If scratching the itch has become an addiction and is damaging your skin, professional psychological advice can help.
- Consider whether food or other allergies could be the cause of your itching, rather than PBC, and ask your doctor to test for these if necessary.
EASL recommends treating pruritus using a stepwise approach. Patients with severe pruritus may have an aggressively ductopenic variant of PBC, with a poor prognosis. EASL recommends the referral of these patients to an expert centre (III, 1).

EASL recommends cholestyramine as the first-line therapy for pruritus, despite its limitations. Attention should be paid to avoid interaction with other medications as a result of its anionic binding resin properties (II-2, 1).

EASL recommends rifampicin as a second-line therapy for pruritus, usually at a dose of 150 mg–300 mg daily. EASL recommends monitoring serum liver tests after initial use (at 6 and 12 weeks following drug initiation) and following dose increase, because of potential hepatotoxicity The agent should be stopped if toxicity is observed (II-2, 1).
Complications - patient awareness

34. EASL recommends considering the risk for osteoporosis in all patients with PBC (III, 1).
35. As part of evaluating the risk of osteoporosis, EASL recommends considering the use of DEXA to assess bone mineral density at presentation and at follow-up where indicated (III, 1).
36. EASL suggests supplementing patients with PBC with calcium and vitamin D, according to local practice (III, 2).
37. Bisphosphonates are safe and effective treatments for patients with PBC and significantly elevated fracture risk from osteoporosis but EASL recommends caution when using them in patients with varices. EASL recommends therapy initiation following specific osteoporosis guidelines (II-2, 1).
38. Fat-soluble vitamin malabsorption can occur in patients with PBC, particularly those with prolonged jaundice. EASL suggests that supplementation should be considered on an individual basis (III, 2).
39. Hyperlipidaemia is a feature of cholestasis, for which there is no substantial evidence to support an elevated cardiovascular risk in patients with PBC. In the subgroup of patients with PBC and metabolic syndrome (with high cholesterol, low HDL cholesterol and high LDL cholesterol levels), EASL suggests considering a pharmacologic approach with cholesterol-lowering agents on a case-by-case basis; treatment is not contraindicated (III, 2).
40. EASL suggests that the Baveno VI guidelines for screening and management of varices apply equally to patients with PBC (III, 2).

PBC can lead to a number of complications. Your doctor can help you manage these in a variety of ways.

Osteoporosis
Osteoporosis is a bone disease that occurs when the body loses too much bone, makes too little bone, or both. As a result, bones become weak and may break from a fall or, in serious cases, from sneezing or minor bumps.

Osteoporosis is a common complication in patients with PBC. You can help to prevent and treat osteoporosis by ensuring you have a good diet, take some weight-bearing exercise, and stop smoking. Your doctor may consider giving you calcium supplements (if you have no history of renal stones) and vitamin D. Several trials have demonstrated that bisphosphonates (drugs that prevent or slow down bone thinning), especially weekly alendronate and monthly ibandronate, are effective in increasing bone mass in patients with PBC.

Hyperlipidaemia
When the concentration of triglycerides or cholesterol in your blood is too high, it is called ‘hyperlipidaemia’. Hyperlipidaemia is normally linked to an increased risk of cardiovascular disease, such as heart attack and angina, stroke, and narrow blood vessels in the legs. But it can also appear because of cholestasis, as part of your PBC, so it does not necessarily mean that your cardiovascular risk is increased.

If you have PBC alongside low HDL cholesterol and high LDL cholesterol levels, we recommend that you take cholesterol-lowering medication as part of a personalised plan.

Veins
Patients with PBC may develop a type of high blood pressure known as ‘portal hypertension’. This affects your hepatic portal system, which is the part of your vein network that directs blood from your intestines to your liver. Portal hypertension is often caused by scar tissue (cirrhosis) that forms in your liver due to inflammation.
Autoimmune hepatitis
Standard management in AIH

*Treatment probably no longer indicated in decompensated, burn-out cirrhosis, unless high inflammatory score on liver biopsy*
Liver cirrhosis at presentation?

- Subclinical disease preceding diagnosis
- 1/3 adults and 1/2 children cirrhosis at diagnosis
- Response in cirrhosis similar, but slower?
- Decompensated cirrhosis? (consider HAI)

Gronbaek et al., 2014
Standard management in AIH

AIH

0.5-1mg/kg/d prednisone

Good Response

Add azathioprine gradually up to 1 – 2 mg/kg/d

Azathioprine-intolerance

second-line therapy (usually MMF)

Taper steroids (ideally trial of steroid withdrawal)

Insufficient response

Consider non-compliance

Consider alternative diagnoses

Increase to 100mg prednisolone i.v.

Manage alternative disease

Response

Insufficient response

Individualize doses (consider checking 6-TG levels) to achieve and maintain normal ALT and IgG

Refer to specialist centre for confirmation of diagnosis, LTX-evaluation and/or alternative immunosuppressives
Treat to what end-point?

- Biochemical remission: normalization of IgG and transaminases
- Histological remission: normal histology or HAI < 4 or equivalent
Withdrawal of treatment?

- Treatment >3 years and >2 years following biochemical remission
- A liver biopsy should be considered prior to treatment withdrawal
- In patients with HAI>3, treatment should not be discontinued
- Surveillance continued life-long (frequently during first 12 months)
- 50-90% of the patients relapse (depending on observation time)
- If relapse occurs, life-long immunosuppression advisable

Montano-Loza et al., 2007
www.easl.eu
“Difficult to treat” AIH

- Intolerance to treatment
  - Azathioprine: Prednisolone monotherapy? Mycophenolate?
  - Prednisolone: Budesonide?
  - Referral for individualized therapy

- Incomplete response
  - Consider diagnosis, concomitant liver disease?
  - Consider compliance (e.g. 6TGN)
  - Increasing the dose of azathioprine to 2 mg/kg/day?
  - Referral for individualized therapy (e.g. CNI, infliximab)
  - Complete response may not be attainable in some patients
Principles of 2nd line therapy

Tolerance ↑

- MMF due to azathioprine side-effects (N = 27)
  - Stop due to pregnancy (N = 1)

- Remission (N = 12)
  - med. dose of MMF: 2.0g/d
  - med. duration of MMF therapy: 24mo.
  - med. min dose of steroids on MMF: 4mg/d
  - med. max dose of steroids on MMF: 12.6mg/d

- No remission (N = 16)
  - med. dose of MMF: 1.6g/d
  - med. duration of MMF therapy: 10mo.
  - med. min dose of steroids on MMF: 6.25mg/d
  - med. max dose of steroids on MMF: 20mg/d

Failure ↓

- MMF due to insufficient response to azathioprine (N = 9)
  - 1 patient excluded due to non-compliance

- Remission (N = 2)
  - med. dose of MMF: 2.0g/d
  - med. duration of MMF therapy: 14mo.
  - med. min dose of steroids on MMF: 12.65mg/d
  - med. max dose of steroids on MMF: 25mg/d

- No remission (N = 6)
  - med. dose of MMF: 1.75g/d
  - med. duration of MMF therapy: 11mo.
  - med. min dose of steroids on MMF: 15g/d
  - med. max dose of steroids on MMF: 18.8mg/d

Hennes et al., 2008
Survey – 2nd line (IAIHG)

- MMF: Total 450, Non-transplant centres 189, Transplant centres 261
- Tacrolimus: Total 115, Non-transplant centres 18, Transplant centres 97
- Ciclosporin: Total 112, Non-transplant centres 17, Transplant centres 95
- Sirolimus: Total 12, Non-transplant centres 0, Transplant centres 12
- Infliximab: Total 12, Non-transplant centres 0, Transplant centres 12
- Rituximab: Total 22, Non-transplant centres 15, Transplant centres 7

Liberal et al., 2017
Liberal et al., 2017

Survey – 2nd line (IAIHG)

Novartis in Phase II: Anti-BAFF (B-cell-activating factor) monoclonal antibody

Liberal et al., 2017
Primary sclerosing cholangitis
Is ursodeoxycholic acid helpful in PSC?

(Olsson et al., 2005)
Is ursodeoxycholic acid harmful in PSC?

(Lindor et al., 2009)
Ursodeoxycholic acid in PSC?

(Karlsen et al., AP&T 2014, IPSCSG survey)
norUDCA in PSC
Obeticholic acid in PSC

Cowdley et al., AASLD 2017
GS-9674 in PSC (non-steroidal FXR)

Trauner et al., AASLD 2018
NGM282 in PSC (FGF19 analog)

**Graph:**
- Mean Pro-C3 (ng/mL) over time for Placebo (n=20), NGM282 1 mg (n=21), and NGM282 3 mg (n=21).

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=20)</th>
<th>NGM282 1 mg (n=21)</th>
<th>NGM282 3 mg (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean AP (U/L)</strong></td>
<td>Day 1: 365</td>
<td>Day 1: 383</td>
<td>Day 1: 354</td>
</tr>
<tr>
<td></td>
<td>Week 12: 355</td>
<td>Week 12: 409</td>
<td>Week 12: 351</td>
</tr>
<tr>
<td></td>
<td>p: 0.78</td>
<td>p: 0.22</td>
<td>p: 0.73</td>
</tr>
<tr>
<td><strong>Mean ALT (U/L)</strong></td>
<td>Day 1: 90</td>
<td>Day 1: 117</td>
<td>Day 1: 96</td>
</tr>
<tr>
<td></td>
<td>Week 12: 86</td>
<td>Week 12: 114</td>
<td>Week 12: 56</td>
</tr>
<tr>
<td></td>
<td>p: 0.26</td>
<td>p: 0.41</td>
<td>p: &lt;0.001</td>
</tr>
<tr>
<td><strong>Mean change in ELF score from baseline</strong></td>
<td>Placebo</td>
<td>NGM282 1 mg</td>
<td>NGM282 3 mg</td>
</tr>
<tr>
<td>From baseline of ≤9.8</td>
<td>0.08</td>
<td>0.12 (p=0.90 vs. placebo)</td>
<td>-0.24 (p=0.23 vs. placebo)</td>
</tr>
<tr>
<td>From baseline of &gt;9.8</td>
<td>-0.01</td>
<td>-0.52 (p=0.016 vs. placebo)</td>
<td>-0.58 (p=0.029 vs. placebo)</td>
</tr>
</tbody>
</table>

Hirschfield et al., EASL 2018
Simtuzumab phase II data

![Graph showing survival free of clinical events percentage over time for SIM 125 mg, SIM 75 mg, and PBO groups.]

<table>
<thead>
<tr>
<th>Number at risk (n)</th>
<th>SIM 125 mg</th>
<th>SIM 75 mg</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>78</td>
<td>75</td>
<td>64</td>
</tr>
<tr>
<td>SIM 125 mg</td>
<td>77</td>
<td>69</td>
<td>57</td>
</tr>
<tr>
<td>SIM 75 mg</td>
<td>79</td>
<td>71</td>
<td>67</td>
</tr>
</tbody>
</table>

p-value vs placebo:
- SIM 125 mg: 0.85
- SIM 75 mg: 0.74
- PBO: 0
Vedolizumab real life data in PSC

Williamson et al., EASL 2018
Antibiotics in PSC – therapy or proof-of-concept?

(a) Clinical trials of antibacterial treatment in primary sclerosing cholangitis

<table>
<thead>
<tr>
<th>Drug (reference)</th>
<th>Year</th>
<th>n</th>
<th>Antibiotic dose</th>
<th>Months of therapy</th>
<th>Change after therapy</th>
<th>ALK</th>
<th>AST</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole (+UDCA) [34]</td>
<td>2004</td>
<td>39</td>
<td>600–800 mg/day</td>
<td>36</td>
<td>−52.4% −41.0% −67.9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minocycline [35]</td>
<td>2009</td>
<td>16</td>
<td>200 mg/day</td>
<td>12</td>
<td>−19.7% −2.8% NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin or metronidazole</td>
<td>2013</td>
<td>18</td>
<td>Vancomycin 125 or 250 mg qid</td>
<td>3</td>
<td>−42% −22% NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>17</td>
<td>Metronidazole 250 or 500 mg tid</td>
<td>3</td>
<td>−10% −9% NA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(b) Case series and reports of antibacterial treatment in primary sclerosing cholangitis

<table>
<thead>
<tr>
<th>Drug (reference)</th>
<th>Year</th>
<th>n</th>
<th>Antibiotic dose</th>
<th>Months of therapy</th>
<th>Change after therapy</th>
<th>ALK</th>
<th>AST</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline [36]*</td>
<td>1959</td>
<td>5</td>
<td>500 mg/day</td>
<td>1–10</td>
<td>−45% −60% −45%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline [27]†</td>
<td>1965</td>
<td>5</td>
<td>500 mg/day</td>
<td>48 (mean)</td>
<td>−21% NA NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole [37]</td>
<td>1983</td>
<td>1</td>
<td>800 mg/day</td>
<td>0.25</td>
<td>NA ‡† NA ‡‡ NA ‡‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine (+UDCA) [38] ††</td>
<td>1998</td>
<td>2†</td>
<td>—</td>
<td>30 and 45</td>
<td>−79% −38% −70%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin [39]</td>
<td>1998</td>
<td>3†</td>
<td>375–1000 mg/day</td>
<td>9 (mean)</td>
<td>NA NA −89%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine (+UDCA) [40]</td>
<td>2002</td>
<td>1</td>
<td>50 mg/kg/day</td>
<td>37</td>
<td>NA NA −92%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine [41]</td>
<td>2006</td>
<td>1</td>
<td>2–4.5 g/day</td>
<td>24</td>
<td>−74% NA −84%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin (+UDCA) [42]</td>
<td>2007</td>
<td>1</td>
<td>500 mg/day, 3 days/week</td>
<td>5</td>
<td>−72% −31% −33%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin [43]</td>
<td>2008</td>
<td>14 ‡</td>
<td>50 mg/kg/day</td>
<td>54 ± 43</td>
<td>NA NA −78%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*(Tabibian et al., 2013)*
Recurrent PSC – role of the colon?

PSC as a model disease for gut-liver interactions

(Hov and Karlsen, Semin Liv Dis 2017)
Four important Kaplan-Meier plots for PSC

- Transplant free survival (Oslo) for years after diagnosis of PSC.
- Proportion without OLT over time (years) with Normal IgG4 and Elevated IgG4.
- Cumulative inc. of HPB malignancy (percent) over time (years) for numbers at risk.

Cholangiocarcinoma surveillance

**Diagnosis of PSC**
- At diagnosis
- Every 6-12 months

- Clinical review
- Serum liver tests
- Tumour marker CA 19-9
- US and/or MRI/MRC, if cirrhosis; US and AFP every six months

**Findings indicating***:
- Malignant stricture
- Development of mass lesion

- ERC with brush cytology ± FISH
- MDT review
- Histological diagnosis if necessary and not contraindicated

*See indicative findings Box 2

**Diagnostic features**

<table>
<thead>
<tr>
<th>Indicative findings</th>
<th>Cholangiocarcinoma</th>
<th>Bile duct dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Clinical:</td>
<td>Rapid clinical deterioration (features of biliary obstruction, weight loss, abdominal pain)</td>
<td>None</td>
</tr>
<tr>
<td>2. Biochemical:</td>
<td>Cholestatic liver function tests</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Continuously elevated CA19-9 after biliary decompression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevated CA-125 (65%)</td>
<td></td>
</tr>
<tr>
<td>3. Non-invasive imaging (MRI/MRC, CT, US)</td>
<td>Mass lesion (iCCA)</td>
<td>Bile duct stricture</td>
</tr>
<tr>
<td></td>
<td>Hilar stricture (pCCA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Distal bile duct stricture (dCCA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>± biliary duct dilatation, extrahepatic metastasis</td>
<td></td>
</tr>
<tr>
<td>4. Invasive imaging: (ERC, POCs, IDUS)</td>
<td>Bile duct stricture or polypoid lesion</td>
<td>Bile duct stricture</td>
</tr>
</tbody>
</table>

**Confirmatory findings**

| 5. Cytological: ± DIA or FISH | High grade dysplasia or carcinoma | Low to high grade dysplasia |
| 6. Histological: (FNAC, biopsy, surgical specimens) | Carcinoma (adenocarcinoma >95% of cases) | Low to high grade dysplasia |

(Karlsen et al., 2017)
Surveillance for malignancy

(Boonstra et al., 2013)
From morphology to molecular diagnoses

Bile – methylation markers

Urine – peptide/protein markers

Blood – microRNA markers

(Karlsen et al. 2017, Eaton et al. 2015, Andresen et al. 2015, Metzger et al. 2013, Bernuzzi et al. 2016)
## Digital medicine and AI

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Images</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiology/Neurology</td>
<td>CT head, acute neuro events</td>
<td>Titanio, Nature Medicine, 2018</td>
</tr>
<tr>
<td></td>
<td>CT head for brain hemorrhage</td>
<td>Arbabshirani, NPJ (Nature) Digital Medicine, 2018</td>
</tr>
<tr>
<td></td>
<td>CT head for trauma</td>
<td>Chilamkurthy, Lancet 2018</td>
</tr>
<tr>
<td></td>
<td>CXR for metastatic lung nodules</td>
<td>Gang Nam, Radiology 2018</td>
</tr>
<tr>
<td></td>
<td>CXR for multiple findings</td>
<td>Singh, PLOS One, 2018</td>
</tr>
<tr>
<td>Pathology</td>
<td>Breast cancer</td>
<td>Bejnordi, JAMA, 2017</td>
</tr>
<tr>
<td></td>
<td>Lung cancer (+ driver mutation)</td>
<td>Coudray, Nature Medicine 2018</td>
</tr>
<tr>
<td></td>
<td>Brain tumors (+ methylation)</td>
<td>Capper, Nature, 2018</td>
</tr>
<tr>
<td></td>
<td>Breast cancer metastases*</td>
<td>Steiner, Am J Surgical Pathology, 2018</td>
</tr>
<tr>
<td></td>
<td>Breast cancer metastases</td>
<td>Liu, Arch Path Lab Med, 2018</td>
</tr>
<tr>
<td>Dermatology</td>
<td>Skin cancers</td>
<td>Esteva, Nature, 2017</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
<td>Haenssle, Annals of Oncology, 2018</td>
</tr>
<tr>
<td></td>
<td>Skin lesions</td>
<td>Han, Journal of Investigative Dermatology</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>Diabetic retinopathy</td>
<td>Gulshan, JAMA, 2016</td>
</tr>
<tr>
<td></td>
<td>Diabetic retinopathy*</td>
<td>Abramoff, NPJ (Nature) Digital Medicine, 2018</td>
</tr>
<tr>
<td></td>
<td>Diabetic retinopathy*</td>
<td>Kanagasingam, JAMA Open 2018</td>
</tr>
<tr>
<td></td>
<td>Congenital cataracts</td>
<td>Long, Nature Biomedical Engineering, 2017</td>
</tr>
<tr>
<td></td>
<td>Retinal diseases (OCT)</td>
<td>De Fauw, Nature Medicine, 2018</td>
</tr>
<tr>
<td></td>
<td>Macular degeneration</td>
<td>Burlina, JAMA Ophthalmology, 2018</td>
</tr>
<tr>
<td></td>
<td>Retinopathy of Prematurity</td>
<td>Brown, JAMA Ophthalmology, 2018</td>
</tr>
<tr>
<td></td>
<td>AMD and diabetic retinopathy</td>
<td>Kermany, Cell, 2018</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>Polyps at colonoscopy*</td>
<td>Mori et al, Annals Internal Medicine, 2018</td>
</tr>
<tr>
<td>Cardiology</td>
<td>Echocardiography</td>
<td>Madani, NPJ (Nature) Digital Medicine, 2018</td>
</tr>
<tr>
<td></td>
<td>Echocardiography</td>
<td>Zhang, Circulation 2018</td>
</tr>
</tbody>
</table>
A changing landscape of liver research

(Karlsen and Tacke, 2018)
A changing landscape of liver research

(Manns et al., Nat Rev Dis Prim 2017)
A changing landscape of liver research

(Manns et al., Nat Rev Dis Prim 2017)
Take home messages

- Treatment in PBC, AIH and PSC is still “antique”
- Second line therapies in PBC: bezafibrate vs. OCA
- Second line therapy in AIH: expert opinion recommendations only
- PSC signals from antibiotics and bile acid therapeutics
- Surveillance and biomarkers challenging, digital medicine and AI