Management of Cholestatic Diseases

2017

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Disclosures

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Lecture fees
Falk Foundation, Gilead, Intercept, Novartis, Roche, Shire, Zambon

Consulting agreements
Intercept, Novartis

Support for investigator-initiated studies
Falk, Intercept
2012 (11): Fever for 3 days, increasing pruritus and progressive jaundice

(Serum liver tests elevated, markers for viral hepatitis, AIH, hereditary metabolic disease neg.)

- No relevant diseases in the past
- Family: no liver disease
- Alcohol: 2 U / week
- Drugs: none
- Medication: oral contraceptives since 15 years
- Work: post office
Physical Examination 2013 (1) 
♀ 34 yrs

- Icteric, exhausted, intermittently scratching woman
- 165 cm, 66 kg
- No other relevant diagnostic findings
<table>
<thead>
<tr>
<th>Test</th>
<th>Reference Value</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>≤ 17 µmol/l</td>
<td>565</td>
<td>(&gt;90% conjugated)</td>
</tr>
<tr>
<td>ALT</td>
<td>≤ 45 U/l</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>≤ 40 U/l</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>γGT</td>
<td>≤ 60 U/l</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>ALP</td>
<td>≤ 120 U/l</td>
<td>347</td>
<td></td>
</tr>
</tbody>
</table>
Diagnostic approach to cholestasis

Detailed history, physical examination, serum liver tests

Elevated ALP + γGT and/or bilirubin

(HBsAg and anti-HCV neg.)

Ultrasound

Dilated ducts, stones, tumor
Abdominal Imaging

♀ 34 yrs

Ultrasound:

- Normal aspect of the liver, no focal lesions
- Sludge in the gallbladder
- No bile duct obstruction (by stones or mass)
Abdominal Imaging

♀ 34 yrs

Ultrasound:
- Normal aspect of the liver, no focal lesions
- Sludge in the gallbladder
- No bile duct obstruction (by stones or mass)

Fibroscan: 17.7 kPa (IQR 3.3, success rate 100%)
CAP: 154 dB/m (IQR 23)
Diagnostic approach to cholestasis

♀ 34 y

Dilated ducts, stones, tumor

EASL CP Guidelines PBC. J Hepatol 2017; submitted
Primary biliary cholangitis* (PBC)

**Characteristics**

**Florid, non-suppurative, destructive cholangitis**

**Women : Men**

9 : 1

**Age at diagnosis**

40 - 60

**Survival without treatment**

7.5-16 years

**Cholestasis**

ALP, γGT ↑

**Autoantibodies**

AMA (anti-PDC-E2)

* Beuers , Gershwin, …Poupon. J Hepatol 2015;63:1285

**Symptoms**

- Fatigue
- Pruritus
- Sicca syndrome
- ...

Sherlock and Summerfield, 1991
Primary biliary cholangitis:

**Potential pathogenetic mechanisms**

- Immune-mediated bile duct injury
- Bile duct injury by hydrophobic bile acids
- Cholestasis with retention of hydrophobic bile acids in liver
- Liver cell damage, apoptosis, necrosis, fibrosis, cirrhosis
- Liver failure

Primary biliary cholangitis (PBC)

Characteristics

- Florid, non-suppurative, destructive cholangitis
- Too low HCO$_3^-$?
- Women : Men
- Age at diagnosis
  - 40 - 60
  - 7.5-16 years
- Survival without treatment
- Cholestasis
- Autoantibodies
  - ALP, $\gamma$GT↑
  - AMA (anti-PDC-E2)

Symptoms
- Fatigue
- Pruritus
- Sicca syndrome
- …
Defect of the biliary HCO$_3$- umbrella:
cholangiocyte injury by BA

Cholestasis with retention of hydrophobic BA in liver

Fibrosis, cirrhosis

Liver failure

Immunologic bile duct injury

Ursodeoxycholic acid (13-15 mg/kg/d)

Liver transplantation

EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
Putative mechanisms and sites of action of UDCA in cholestatic liver diseases

Stimulation of hepatocellular secretion

Stimulation of cholangiocytes

Biliary HCO$_3^-$ umbrella

Bile acids

Apoptosis
Necrosis

Antiapoptotic effects

Reduction of Bile toxicity

Bile acids

Beuers et al., Hepatology 2010;52:1489
Chang JC et al. Hepatology 2016; 64:522
The PBC GLOBE score predicts outcome after 1 year of UDCA

**GLOBE score**: Age, bilirubin, alkaline phosphatase, albumin, platelets

Lammers et al., Gastroenterology 2015;149:1804
Primary biliary cholangitis:

**Potential pathogenetic mechanisms**

- Immunologic bile duct injury
- Defect of the biliary HCO$_3^-$ umbrella: cholangiocyte injury by BA
- Cholestasis with retention of hydrophobic BA in liver
- Fibrosis, cirrhosis
- Liver failure

**Potentially new Therapy**

- Ursodeoxycholic acid (13-15 mg/kg/d)
- FXR agonists: e.g. obeticholic acid
- GR/PXR agonists: e.g. budesonide?
- PPAR$\alpha$ agonists: e.g. bezafibrate?

- Liver transplantation

EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
Obeticholic acid improves serum alkaline phosphatase (ALP) in PBC

Phase 3

Mean ± SEM

Diagnostic approach to cholestasis

1. Detailed history, physical examination, serum liver tests

2. Elevated ALP + γGT and/or bilirubin
   - Ultrasound
     - Normal
       - AMA + ANA (sp100, gp210)
       - MRCP/EUS
     - Negative
       - Dilated ducts, stones, tumor
       - PBC
       - PSC, SSC

♀ 34 y

EASL CP Guidelines PBC. J Hepatol 2017; submitted
Primary sclerosing cholangitis

The typical patient in the Netherlands

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Point prevalence</td>
<td>6.0</td>
</tr>
<tr>
<td>Incidence</td>
<td>0.5</td>
</tr>
<tr>
<td>Age at manifestation</td>
<td>38.9</td>
</tr>
<tr>
<td>Male gender</td>
<td>64%</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>68%</td>
</tr>
<tr>
<td>UDCA treatment</td>
<td>92%</td>
</tr>
<tr>
<td>LTx-free survival</td>
<td>21.2</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>7%</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>3%</td>
</tr>
</tbody>
</table>

Boonstra, Ponsioen et al., Hepatology 2013;58:2045 (population-based cohort [n=590, follow-up 92 months] covering the Northern half of the Netherlands)
Pathogenetic model

Immunologic bile duct injury (Cytokine-mediated)

Bile duct stenoses
Aggravation of injury by BA

Cholestasis with retention of hydrophobic bile acids in liver

Fibrosis, cirrhosis

Liver failure

Ursodeoxycholic acid (15-20 mg/kg/d)

Liver transplantation

EASL CP Guidelines, J Hepatol 2009;51:237
Bile duct stenoses
Aggravation of injury by BA
Cholestasis with retention of hydrophobic bile acids in liver
Fibrosis, cirrhosis
Liver failure

PSC: Pathogenetic model

Immunologic bile duct injury
(Cytokine-mediated)

Endoscopic dilatation

Vedolizumab? norUDCA?

RCT (Phase 2)

Ursodeoxycholic acid
(15-20 mg/kg/d)

RCT (Phase 3)

Nuclear receptor agonists?
- PPARα

RCT (Phase 2)

FGF19 homologues?

Liver transplantation

Therapy under evaluation
The Patient with Sclerosing Cholangitis

Diagnostic Algorithm

History, additional diagnostic procedures:
Causes of secondary sclerosing cholangitis?

- Bile duct surgery
- Abdominal trauma
- Choledocholithiasis *
- Cholangiocarcinoma *
- Recurrent pancreatitis
- Ischemic cholangitis
- Eosinophilic cholangitis
- Mastcell cholangiopathy
- AIDS cholangiopathy
- Recurrent pyogenic cholangitis
- Portal hypertensive biliopathy
- IgG4-assoc. cholangitis (IAC)
- ABCB4 deficiency
- others

* may be consequence of PSC

EASL Clinical Practice Guidelines, J Hepatol 2009;51:237
IgG4-associated cholangitis mimics PSC and CCA

Cholangiographic appearance mimicking primary sclerosing cholangitis (PSC)

Cholangiographic appearance mimicking cholangiocarcinoma (CCA)

Misdiagnosis is common!

Hubers & Beuers, Viszeralmedizin 2015;31:185
Diagnostic value of serum IgG4 is limited

Sensitivity = 86%
Specificity = 75%

Kruskal-Wallis test: p<0.0001


n=125

CA: Biliary and pancreatic malignancies
Distinguishing PSC and IgG4-associated cholangitis

The most prominent IgG4+ BCR clone ranks higher in IgG4-RD than PSC

Sensitivity = 100%
Specificity = 100%

Rank of the most prominent IgG4+ BCR clone (detected by NGS) among all IgG clones

Doorenspleet, Hubers et al. Hepatology 2016; 64: 501
BCR: B-cell receptor
CA: Biliary and pancreatic malignancies

Maillette de Buy Wenniger, Doorenspleet et al. Hepatology 2013; 57: 2340
Distinguishing PSC and IgG4-associated cholangitis

The most prominent IgG4+ BCR clone ranks higher in IgG4-RD than PSC

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Sensitivity = 100%
Specificity = 100%

Doorenspleet, Hubers et al. Hepatology 2016; 64: 501

Maillette de Buy Wenniger, Doorenspleet et al. Hepatology 2013; 57: 2340

CA: Biliary and pancreatic malignancies
Distinguishing PSC and IgG4-Related Disease
An affordable IgG4/IgG RNA qPCR is almost as accurate as NGS technology

Sensitivity = 94%
Specificity = 99%

Doorenspleet, Hubers et al. Hepatology 2016; 64: 501
n=125
CA: Biliary and pancreatic malignancies
Chronic Exposure to Occupational Antigens May Play a Key Role in the Initiation and/or Maintenance of IgG4-Related Disease

“Blue collar” work
(> 1 year, mostly lifelong)
IAC/AIP (n=25 and 44, resp.)
88 %
Amsterdam
61 %
Oxford
PSC (n=21 and 22, resp.)
16 %

Maillette de Buy Wenniger, Curver, Beuers. Hepatology 2014: 60:1453
Diagnostic approach to cholestasis

Female 34 yrs

Detailed history, physical examination, serum liver tests

Elevated ALP + \( \gamma \)GT and/or bilirubin

Ultrasound

Dilated ducts, stones, tumor

Normal

AMA + ANA (sp100, gp210)

PBC

Negative

MRCP/EUS

PSC, SSC

Negative

Liver biopsy

Parenchymal disease

ERCP?

EASL CP Guidelines PBC. J Hepatol 2017; under review
Liver biopsy

♀  34 yrs
dd toxic / canalicular transport defect?

Courtesy of Dr. J. Verheij
Diagnostic approach to cholestasis

Detailed history, physical examination, serum liver tests

Elevated ALP + γGT and/or bilirubin

Ultrasound

- Dilated ducts, stones, tumor

Normal

AMA + ANA (sp100, gp210)

- PBC

Negative

MRCP/EUS

- PSC, SSC

Negative

Liver biopsy

- Parenchymal disease

Negative

Genetic analysis

- ABCB4 def., (ABCB11, ATP8B1, etc)

♀ 34 yrs

EASL CP Guidelines PBC. J Hepatol 2017; under review
Consequences of canalicular transporter defects

**Transporter** | **Gene**  
---|---  
FIC1 | *ATP8B1*  
BSEP | *ABCB11*  
MDR3 | *ABCB4*  

**PFIC:** Progressive familial intrahepatic cholestasis  
**LPAC:** Low phospholipid associated cholelithiasis  
**BRIC:** Benign recurrent intrahepatic cholestasis  
**ICP:** Intrahepatic cholestasis of pregnancy  
**PHSF:** Persistent hepatocellular secretory failure
Heterozygote mutation in the $ABCB11$ gene (c.2809G>A) compatible with:

Persistent hepatocellular secretory failure (PHSF)

(i) Serum bilirubin $>255 \mu$mol/L
(ii) Persistently elevated bilirubin ($>1$ week) after removal of the underlying cause (medication, toxin, transient mechanical obstruction)
(iii) Exclusion of bile duct obstruction by imaging
(iv) No underlying liver disease

van Dijk et al. Liver Int 2015; 35:1478
Treatment of PHSF

Rifampicin 300mg/day

Weeks after start treatment

♀ 34 yrs
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