
2023
SCSG
LIVER SYMPOSIUM
DECEMBER 9-10, 2023

Difficult Cases in Cholestatic Liver Disease

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Disclosures

- I have no relevant financial relationship with ineligible companies
- The content of my material(s)/presentation(s) will include discussion of unapproved or investigational uses of products or devices

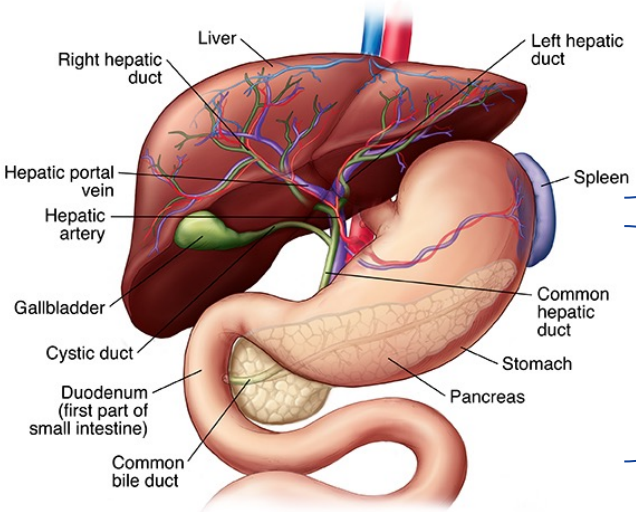
Outline

- Diagnostic Challenges in Intrahepatic Cholestasis
- Biliary stricture in Primary Sclerosing Cholangitis
- Management of Cholestatic Itch

Case 1: New Diagnosis of Cholestasis

- 51-year-old woman referred for evaluation of abnormal liver tests. She notes ~2 months of diffuse itching, worse at night.
- PMHx: prediabetes, anxiety, hypothyroidism, obesity, hyperlipidemia, chronic fatigue
- PSHx: laparoscopic cholecystectomy 20 years ago, cesarian section x 2
- Medications: metformin, citalopram, levothyroxine, atorvastatin, vitamin D. Started taking Ashwagandha for fatigue 3 months ago.
- Social: Married, 2 children, works as a schoolteacher. Alcohol use is 4 glasses of wine per week. No tobacco or drug use.
- No known family history of liver disease
- Physical exam notable for diffuse excoriations, scattered telangiectasias, and mild hepatomegaly without tenderness, spleen not palpable
- Labs: ALT 54, AST 48, ALP 327, TB 0.9
- US: No biliary dilatation, coarse echogenicity of parenchyma

Cholestatic Liver Disease

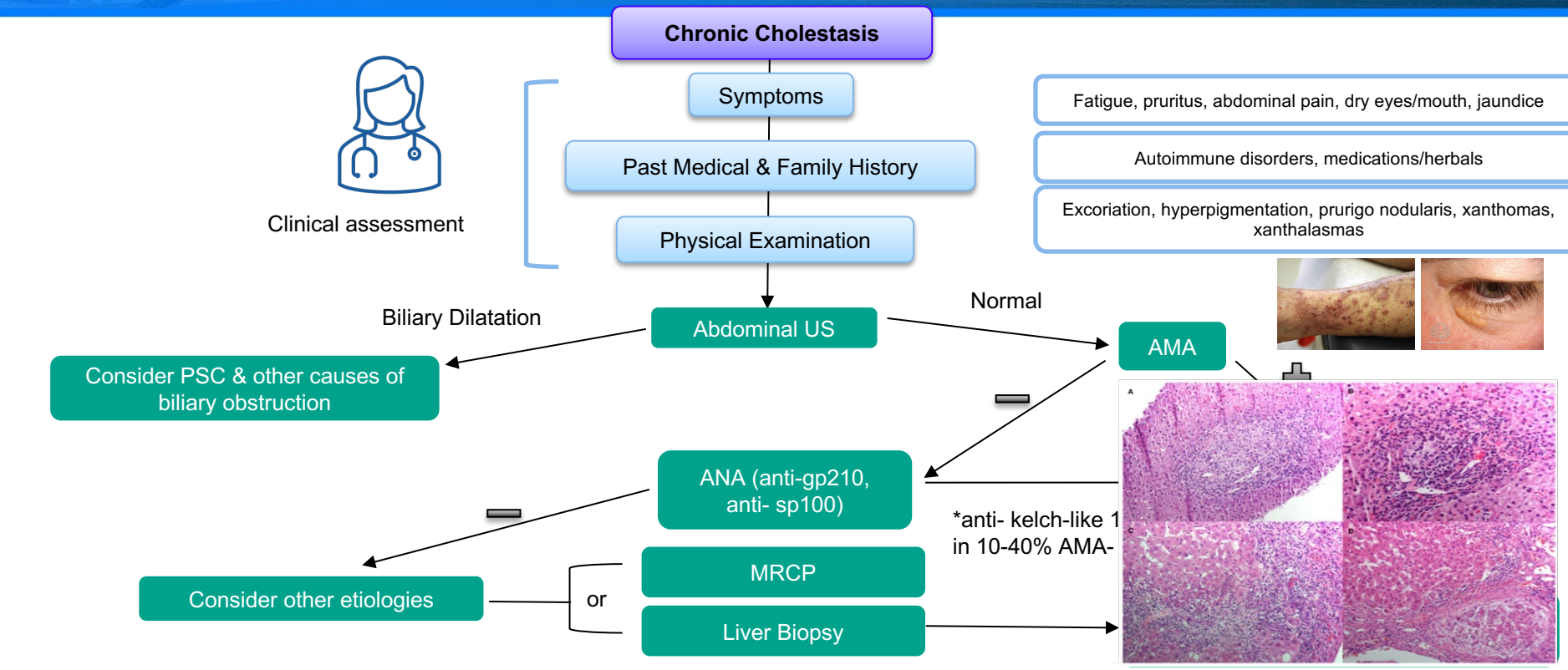


Intrahepatic

Autoimmune (PBC, PSC)
DILI
Benign recurrent intrahepatic cholestasis (BRIC)
Sepsis
Infiltrative diseases
Congestive hepatopathy
Cholestasis of Pregnancy
TPN
Liver allograft rejection
Alagille syndrome
Progressive familial intrahepatic cholestasis (PFIC)

Extrahepatic

Primary Sclerosing Cholangitis
Secondary Sclerosing Cholangitis
Malignant obstruction
Liver flukes
Choledocholithiasis
Biliary atresia



Hepatology Communications. 7(6):e0179, June 2023; *Hepatology.* Vol.69, No.1, 2019.

Drug Induced Cholestasis

1. Cholestatic pattern of serum enzyme elevations (R value <2), with Alkaline Phosphatase levels greater than 3 times ULN (>345 U/L) at the time of peak ALT or bilirubin elevation
2. Latency of 2 to 24 weeks
3. Symptoms (if present) of dark urine or pruritus early during course
4. Bilirubin >2.5 mg/dL
5. If liver biopsy is obtained, changes of intrahepatic cholestasis with inflammatory cells but mild to moderate focal hepatocellular necrosis
6. Exposure to an agent known to cause cholestasis

R value = (ALT ÷ ULN)/(ALP ÷ ULN)

Examples: rifampin, penicillins, amoxicillin/clavulanate, cephalosporins, sulfonylureas, methimazole

https://www.ncbi.nlm.nih.gov/books/NBK548914/.

Ashwagandha-induced liver injury—A case series from India and literature review. Philips, Cyriac A.; Valsan, Arun; Theruvath, Arif H.; Ravindran, Resmi; Oommen, Tharun T.; Rajesh, Sasidharan; Bishnu, Saptarshi; Augustine, Philip; on behalf of The Liver Research Club India. *Hepatology Communications.* 7(10):e0270, October 2023.

Case 2: Symptomatic Biliary Stricture

- 69-Year-old man with history of Crohn's disease diagnosed in 2015 with cholestatic liver test abnormality first noted 2/2022.
- PMHx: Ileal Crohn's Disease, Prostate cancer (radiation), HTN, LTB, hyperlipidemia
- PSHx: None
- Medications: Adalimumab, Amlodipine, Atorvastatin, and UDCA
- Social: 6 beers/day, ½ PPD tobacco
- Exam: BMI 21, no stigmata of chronic liver disease
- Labs: AST 216, ALT 450, ALP 775, TB 2.7, Alb 3.9; CA 19-9; IgG4 60; CA 19-9 125

*There is i**ntrahepatic biliary duct dilatation**, and **dilation of the common bile duct** measuring approximately 12 mm. Moderate left i**ntrahepatic biliary duct dilatation**, mild on the right. However, the common hepatic duct shows normal caliber with T2 hypointense soft tissue surrounding it. This **soft tissue shows enhancement,** which has decreased in size when compared to prior CT.*

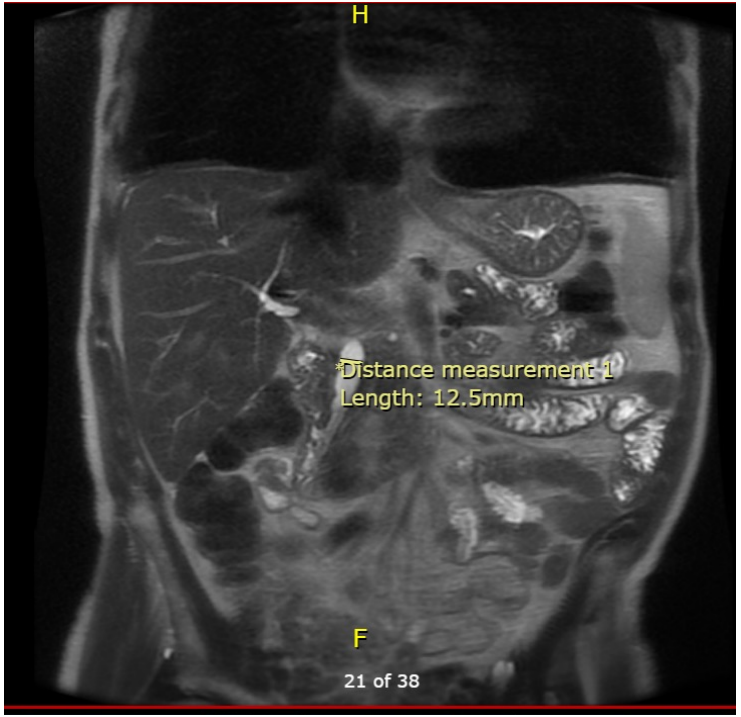
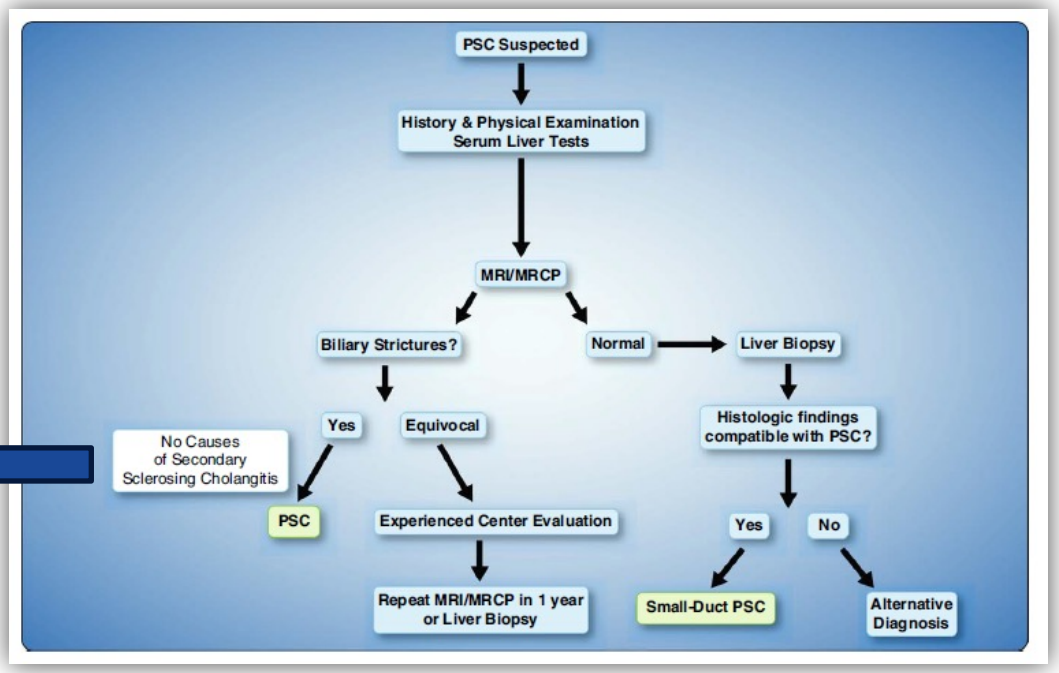


TABLE 2 Etiologies of secondary sclerosing cholangitis

Infectious	HIV-related cholangiopathy Recurrent pyogenic cholangitis Cholangitis lenta or subacute nonsuppurative cholangitis Parasitic cholangiopathy • Hydatid cyst • Echinococcosis • Clonorchiasis and opisthorchiasis • Ascariasis • Fascioliasis • Schistosomiasis
Ischemic	Critically ill patients Hereditary hemorrhagic telangiectasis Intra-arterial chemotherapy Hepatic artery thrombosis
Malignant	Cholangiocarcinoma Diffuse intrahepatic metastasis Langerhans cell histiocytosis Lymphoma
Autoimmune	Eosinophilic cholangitis Hepatic inflammatory pseudotumor IgG4-associated cholangitis Mast cell cholangiopathy Sarcoidosis
Anatomic	Choledocholithiasis Intrahepatic lithiasis Cystic fibrosis liver disease Surgical biliary trauma Anastomotic stricture Portal hypertensive biliopathy Recurrent pancreatitis Sickle cell cholangiopathy Choledochal cyst
Drug-induced	Immunotherapy with checkpoint inhibitors • Pembrolizumab • Nivolumab • Atezolizumab



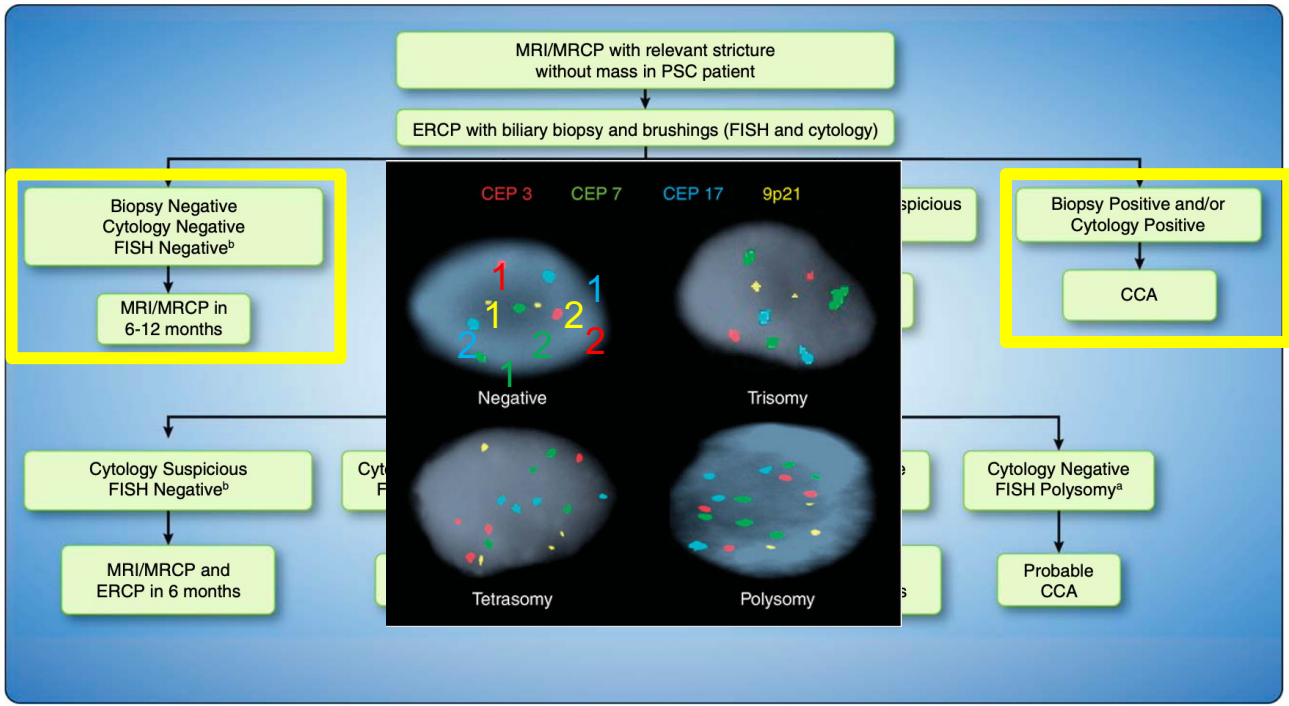
Hepatology. 2023;77:659–702.

Updated Terminology

TABLE 1 Definitions in PSC

PSC	Chronic, cholestatic liver disease likely of autoimmune origin characterized by inflammation and fibrosis of intrahepatic and/or extrahepatic bile ducts, leading to the formation of bile duct strictures, and frequently associated with IBD
Small-duct PSC	Less common variant of PSC that is characterized by typical cholestatic and histological features of PSC but with normal bile ducts on cholangiography
PSC–AIH overlap	Concurrent diagnostic features of PSC and clinical, biochemical, and histological features of AIH
Secondary sclerosing cholangitis	Biliary strictures due to identifiable causes that can result in secondary biliary cirrhosis
IgG4 sclerosing cholangitis	Biliary strictures due to elevated IgG4-positive plasma cells in tissue and serum IgG4 elevation frequently associated with pancreatic involvement
Dominant stricture	A biliary stricture on ERCP with a diameter of $\leq$1.5 mm in the common bile duct or of $\leq$1 mm in the hepatic duct
High-grade stricture	A biliary stricture on MRI with cholangiopancreatography with >75% reduction in the common bile duct or hepatic ducts
Relevant stricture	Any biliary stricture of the common bile duct or hepatic ducts associated with signs or symptoms of obstructive cholestasis and/or bacterial cholangitis

Hepatology. 2023;77:659–702.

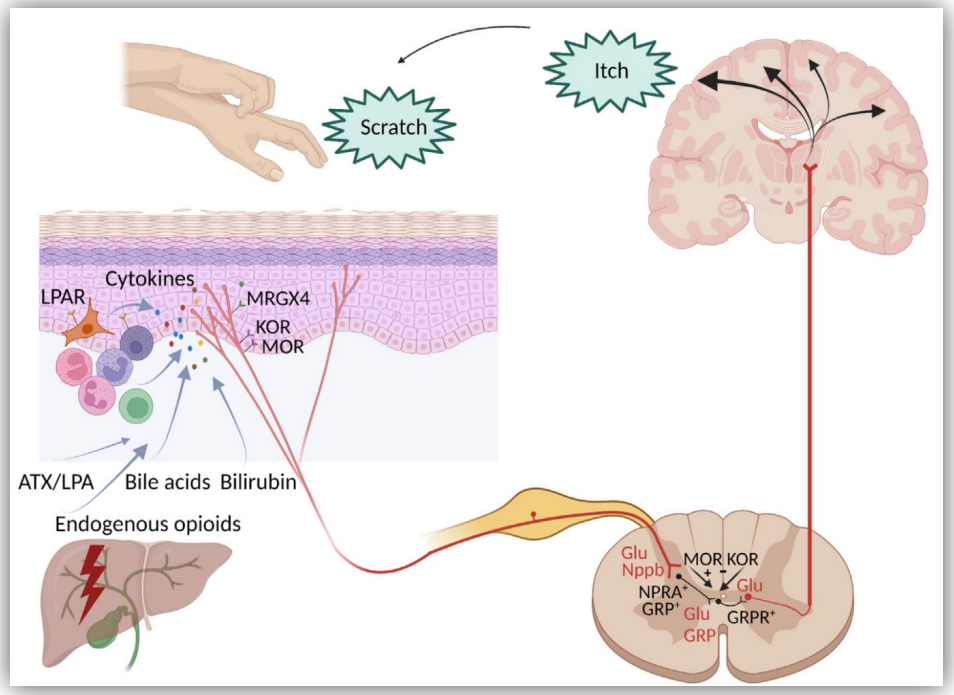


Am J Gastroenterol. 2015 Feb; 110(2): 299–309; *Hepatology*. 2023;77:659–702.

Case 3: Cholestatic Itch

- 60-year-old male veteran diagnosed with 12 cm intrahepatic CCA in 2019 s/p PV embolization, extended right hepatectomy, adjuvant chemo/radiation. In 2021 he was treated with SBRT to presumed adrenal mets. Otherwise, no CCA recurrence but extensive complications (enteric strictures, vascular strictures, SOS-like picture in liver remnant) and refractory cholestatic itch.
- Therapies tried to date: UDCA, sertraline, antihistamines, naltrexone, cholestyramine, therapy, various emollients, sleep aids, light therapy
- Labs: ALT 84, AST 141, ALP 323, TB 22, CA 19-9 160 (pre-treatment 4156)
- Imaging: Stable post-op changes from hepatectomy, cholecystectomy, hepaticojejunostomy. Mild intrahepatic biliary dilatation. Persistent heterogeneous and mottled appearance of the liver remnant.

Pathogenesis of cholestatic pruritus is incompletely understood



Basic tenants of management

Assess

- Do you have itching?
- How does itching interfere with your lifestyle?
  - Does it affect your sleep or activities?
  - Do you bleed from scratching?
- Would you like treatment for the itching?

Manage

- First line: cholestyramine, bezafibrate where available
- Second line: rifampin, naltrexone (or other opioid antagonists), sertraline
- Third line (for extreme itching): plasmapheresis
- Experimental: butorphanol spray, UV light therapy
- Clinical trials
- Last resource: liver transplantation

Clin Liver Dis. 26 (2022) 727–745; *Clinical Gastroenterology and Hepatology*. 2023;21:2076–2087.

Table 1
Systemic pharmacologic treatment options for pruritus in patients with primary biliary cholangitis.

	Cholestyramine	Rifampicin	Bezafibrate	Naltrexone	Sertraline	Gabapentin
Label	In-Label	Off-Label	Off-Label	Off-Label	Off-Label	Off-Label
Starting dose	4 g/d	150 mg/d	(200–)400 mg/d	12.5 mg/d (or low-dose naloxone)	50 mg/d	100–300 mg/d
Max. recommended dose	16 g/d	450–600 mg/d	400 mg/d	150 mg/d	100 mg/d	3600 mg/d
AE/interactions	Interference with intestinal absorption of other medication, in particular UDCA and fat-soluble vitamins (such as vitamin A, D, E, and K)	• Induction of hepatic enzymes→altered metabolism of other drugs (eg, oral anticoagulants, oral contraceptives, antiepileptic drugs) • Hepatotoxicity in up to 5% of patients • Orange-red–colored body fluids	• Dose reduction in case of impaired renal function, contraindicated in dialysis patients • Risk of myopathy as well as increased risk of rhabdomyolysis with concomitant statin use • In long-term treatment: hepatotoxicity in up to 5% of patients	AE: opioid-like withdrawal reactions (low starting dose, eg, 12.5 mg/d or naloxone), increased pain sensations, confusion	AE: hyponatremia, QT prolongation, nausea, vomiting, sleep disturbance, restlessness, change in appetite	AE: dizziness, somnolence, falls with risk of fractures, headaches • Dose reduction in case of impaired renal function, very careful use in dialysis patients (max. 100 mg/d)
Advice	• 2- to 4-h interval to oral intake of other medication • Change to other drugs if not effectively treating pruritus after 2 wk	• Doses of 150–300 mg/d often sufficient • Monitoring of transaminases after 2, 6, and 12 wk, afterward in 12-wk intervals and in case of dose changes	• Monitoring of transaminases, creatine kinase, and retention parameters after 2, 6, and 12 wk, afterward in 12-wk intervals • Fenofibrate as less effective alternate	For in-patients or in case of severe pruritus: intravenous application of naloxone (0.002–0.2 μg/kg/min; bolus of 0.4 mg if necessary), subsequent switch to naltrexone	• Regular monitoring of sodium • ECG with QT time monitoring • Paroxetine, mirtazapine, and other SSRI may also be applied as alternates	• Regular monitoring of retention parameters • Pregabalin as alternate drug (use doses of 75–600 mg/d)

Clin Liver Dis. 26 (2022) 727–745.

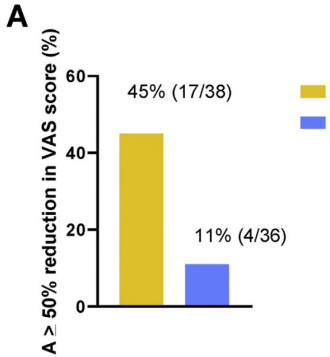
Fibrates for Itch (FITCH) in Fibrosing Cholangiopathies: A Double-Blind, Randomized, Placebo-Controlled Trial

BEZAFIBRATE is a broad peroxisome proliferator-activated receptor (PPAR) agonist with anticholestatic, anti-inflammatory and antifibrotic properti

Patients with moderate analog scale [VAS]) due

Randomized 1:1 to Bez

The primary end point v



Gastroenterology. 2021 160734-743.e.

Intercept

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Press Release

Intercept Pharmaceuticals Receives FDA Orphan Drug Designation for the Fixed-Dose Combination of OCA and Bezafibrate for the Treatment of Primary Biliary Cholangitis (PBC)

May 16, 2023

PDF Version

Company on track to complete planned interim analyses from two ongoing Phase 2 studies of the OCA-bezafibrate combination in 2023

Results from planned interim analysis of Phase 2 study evaluating the effects of OCA and bezafibrate on serum biomarkers in PBC to be presented at EASL Congress 2023

(Nasdaq: ICPT), a biopharmaceutical company focused on the development and

Table 1. Demographic, Clinical, and Biochemical Characteristics at Baseline for Each Group

	Placebo (n = 36)
	13
	23
	(41–59)
	15
	19
	2
	11
	27
	8
	7
	4
	0
	(10–36)
	169–636)
	101–539)
	(49–91)
	36–148)

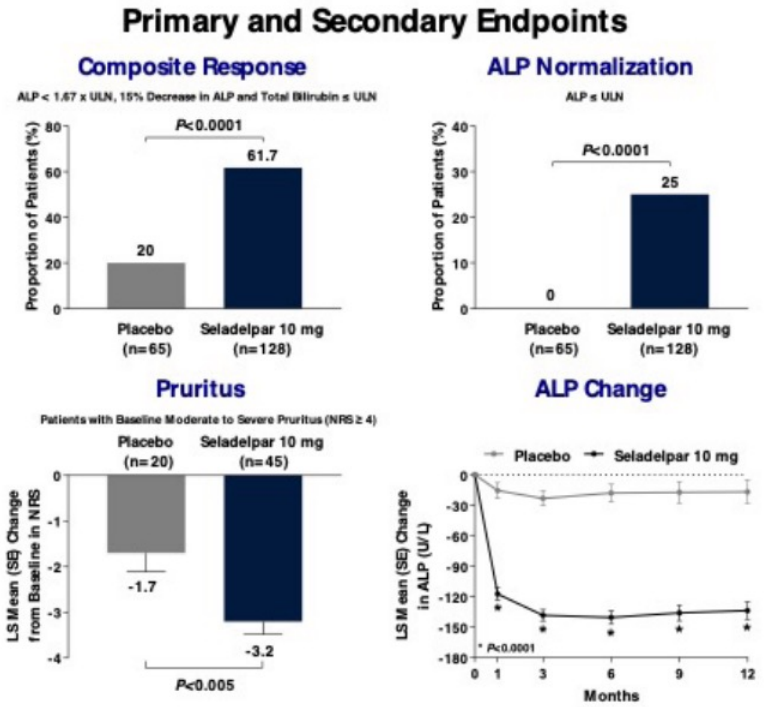
No serious safety events were identified.

Seladelpar

- Selective, potent **PPAR-delta agonist**
- **Anti-cholestatic, anti-inflammatory, anti-pruritic activities**
- **RESPONSE** trial
  - 12-month, placebo-controlled RCT
  - Seladelpar 10mg
  - Seladelpar 5 mg for 6 months with titration up to 10 mg based on tolerability and response
- **Eligibility**: UDCA treatment ≥ 12 months (or intolerance) with ALP ≥ 1.67 x ULN and TB ≤ 2 x ULN
- **Participants**: N=193, 94.8% female, age 56.7 years, 94% on UDCA, mean ALP 314 U/L, TB 0.76 ml/dL, mean NRS 3.0

Hirschfield et al. Abstract 5002. TLM 2023.

Pruritus Numeric Rating Scale (NRS)
0 ⟷ 10



Hirschfield et al. Abstract 5002. TLM 2023.

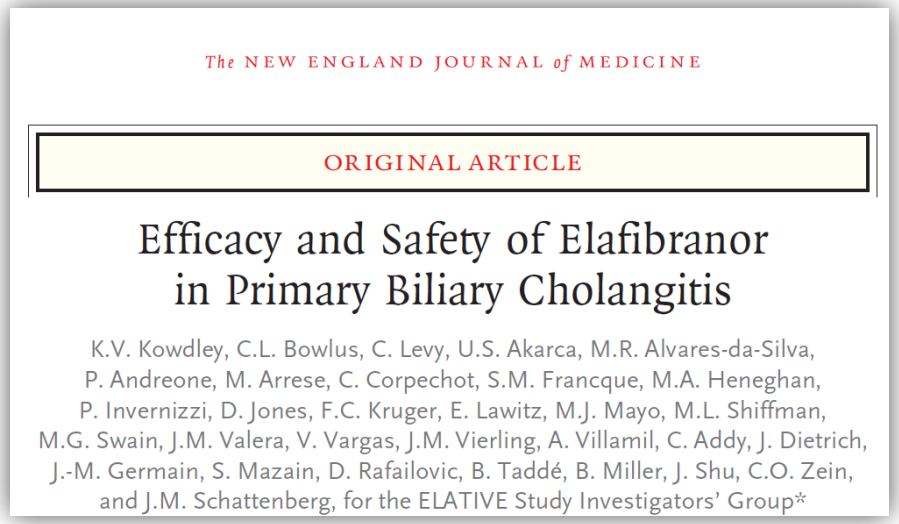
"*The decision by the FDA to grant Breakthrough Therapy designation emphasizes the significant impact of pruritus on day-to-day functioning for people living with PBC and underscores the potential of seladelpar to help fill a critical need for a treatment that both significantly reduces markers of cholestasis and pruritus in patients with PBC, including those with compensated cirrhosis,*"

Seladelpar Granted Revised Breakthrough Therapy Designation for the Treatment of Primary Biliary Cholangitis Including Pruritus in Patients Without Cirrhosis or With Compensated Cirrhosis

October 23, 2023 8:00am EDT

Download as PDF

NEWARK, Calif., Oct. 23, 2023 (GLOBE NEWSWIRE) -- CymaBay Therapeutics, Inc. (NASDAQ: CBAY), a biopharmaceutical company focused on innovative therapies for patients with liver and other chronic diseases, today announced that the U.S. Food and Drug Administration (FDA) has revised the originally granted Breakthrough Therapy Designation for seladelpar to now reflect treatment of primary biliary cholangitis (PBC) including pruritus in adults without cirrhosis or with compensated cirrhosis (Child Pugh A). Seladelpar is the only potent, selective, orally active PPARδ agonist, or delpar, with phase 3 results demonstrating a statistically significant improvement in PBC-related cholestatic pruritus.



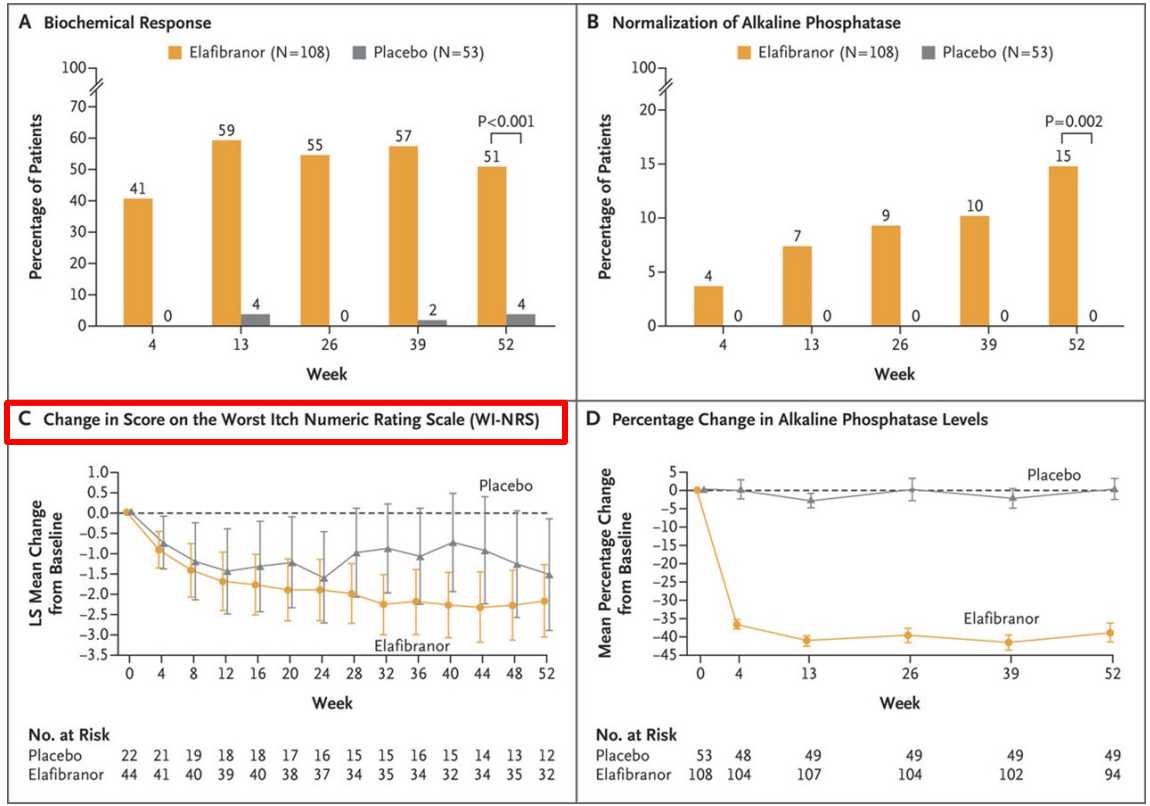
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis

K.V. Kowdley, C.L. Bowlus, C. Levy, U.S. Akarca, M.R. Alvares-da-Silva, P. Andreone, M. Arrese, C. Corpechot, S.M. Francque, M.A. Heneghan, P. Invernizzi, D. Jones, F.C. Kruger, E. Lawitz, M.J. Mayo, M.L. Shiffman, M.G. Swain, J.M. Valera, V. Vargas, J.M. Vierling, A. Villamil, C. Addy, J. Dietrich, J.-M. Germain, S. Mazain, D. Rafailovic, B. Taddé, B. Miller, J. Shu, C.O. Zein, and J.M. Schattenberg, for the ELATIVE Study Investigators' Group*

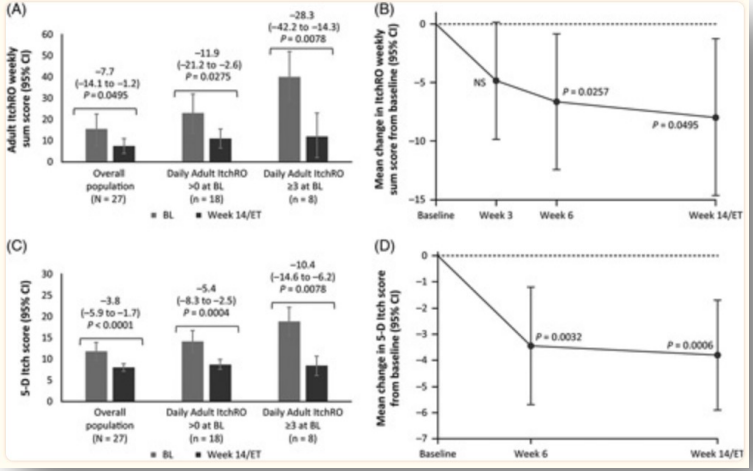
- Oral, dual peroxisome proliferator-activated receptor (PPAR)-alpha/delta agonist
- **ELATIVE** trial
  - Phase 3, 12-month, placebo controlled RCT
  - Elafibranor 80mg daily (N=108)
  - Placebo (N=53)
- **Eligibility**: Inadequate response or intolerance to UDCA, ALP ≥ 1.67 x ULN, TB ≤ 2 x ULN, no AIH overlap, no decompensation
- **Participants:** N=161, 96% female, age 57 years, ALP 322 U/L, TB 9.6 mmol/L, LSM 10 kPa, WI-NRS 3.3


A Biochemical Response
Elafibranor (N=108)
Placebo (N=53)
Percentage of Patients
P<0.001
41
0
59
4
55
0
57
2
51
4
4
13
26
39
52
Week
B Normalization of Alkaline Phosphatase
Elafibranor (N=108)
Placebo (N=53)
Percentage of Patients
P=0.002
4
0
7
0
9
0
10
0
15
0
Week
C Change in Score on the Worst Itch Numeric Rating Scale (WI-NRS)
LS Mean Change from Baseline
Placebo
Elafibranor
Week
No. at Risk
Placebo 22 21 19 18 18 17 16 15 15 16 15 14 13 12
Elafibranor 44 41 40 39 40 38 37 34 35 34 32 34 35 32
D Percentage Change in Alkaline Phosphatase Levels
Mean Percentage Change from Baseline
Placebo
Elafibranor
Week
No. at Risk
Placebo 53 48 49 49 49 49
Elafibranor 108 104 107 104 102 94

Safety, Tolerability, and Efficacy of MARALIXIBAT in Adults With Primary Sclerosing Cholangitis

Bile acids are crucial mediators of liver injury in cholestatic liver disease and have long been proposed as a key pruritogen.

- Intestinal reabsorption of BAs occurs in the terminal ileum through the ileal bile acid transporter (**IBAT**)
- Maralixibat is a potent, selective, and minimally absorbed inhibitor of IBAT. Interruption of BA recirculation with IBAT inhibitors reduces intestinal BA reabsorption and increases mean fecal BA excretion up to 8-fold.
- Maralixibat is FDA approved for cholestatic itch in Alagille syndrome



Open-label, phase 2, safety, tolerability, and efficacy study of maralixibat in adults with PSC.

14-week treatment period comprised a 6-week dose-escalation phase and an 8-week stable-dosing phase.

Gastrointestinal treatment-emergent adverse events (TEAEs) occurred in 81.5%, with diarrhea in 51.9%.

Bowlus et al. *Hepatology Communications.* 7(6):e0153, June 2023.

Summary

- Diagnostic evaluation of cholestatic liver disease should include imaging, careful assessment for medication exposures, and autoantibodies
- Updated guidance on PSC from AASLD includes detailed guidance on evaluation of relevant biliary strictures
- Pipeline therapies for cholestatic liver disease hold promise for disease control as well as improved cholestatic itch compared to currently approved therapies (UDCA, OCA)
- IBAT inhibitors, currently approved for Alagille syndrome, may also improve control of cholestatic itch in other etiologies

Thank You

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