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Cholestatic Disease

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Disclosures

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Disclosures

Glenda Quinones, DNPc, NP-C

Advisory Board: Intercept, Clinical Area – PBC

Advisory Board: AbbVie, Clinical Area – IBD

Primary Biliary Cholangitis (PBC)

- Previously known as Primary Biliary Cirrhosis
- PBC is an immune-mediated cholestatic liver disease[1]
- Present in adults. More commonly after age of 40 and predominately females. Mean age at presentation in 52
- Incidence and prevalence is increasing across the globe[2]
- PBC can lead to liver fibrosis, cirrhosis and complications of end-stage liver disease if left untreated[1]

1. Hirschfield et al. *Expert Review of Gastroenterology and Hepatolgy.* 2021 Jul 7;1-11. doi: 10.1080/17474124.2021.1945919;
2. Trivedi et al. *Gut*. 2021 Jul 15;gutjnl-2020-322362. doi: 10.1136/gutjnl-2020-322362.

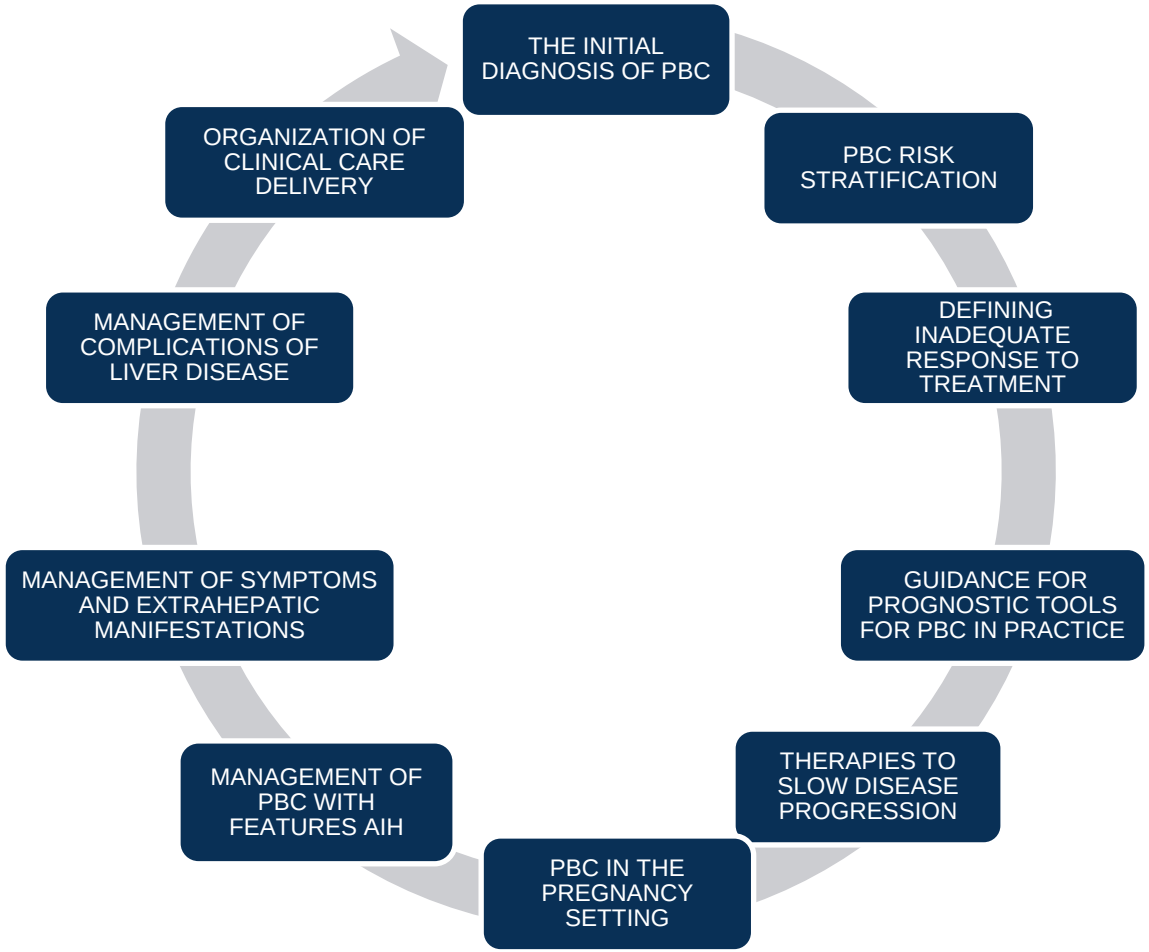
PBC Phenotype

Age	Usually >40 years
Gender	Female > Male (9:1)
Serology	AMA in ~95%; disease-specific ANA in ~30%-50%; ASMA may be present
Immunoglobulin	IgM typically elevated
MRCP	Normal
Liver Histology	Lymphocytic infiltrate; inflammatory duct lesion; granuloma may be present
Coexisting IBD	Not typical
Clinical Symptoms	Itching and fatigue

Abbreviations: AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth-muscle antibody; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiography; PBC, primary biliary cholangitis.

Trivedi PJ et al. *Aliment Pharmacol Ther*. 2012;36:517-533.

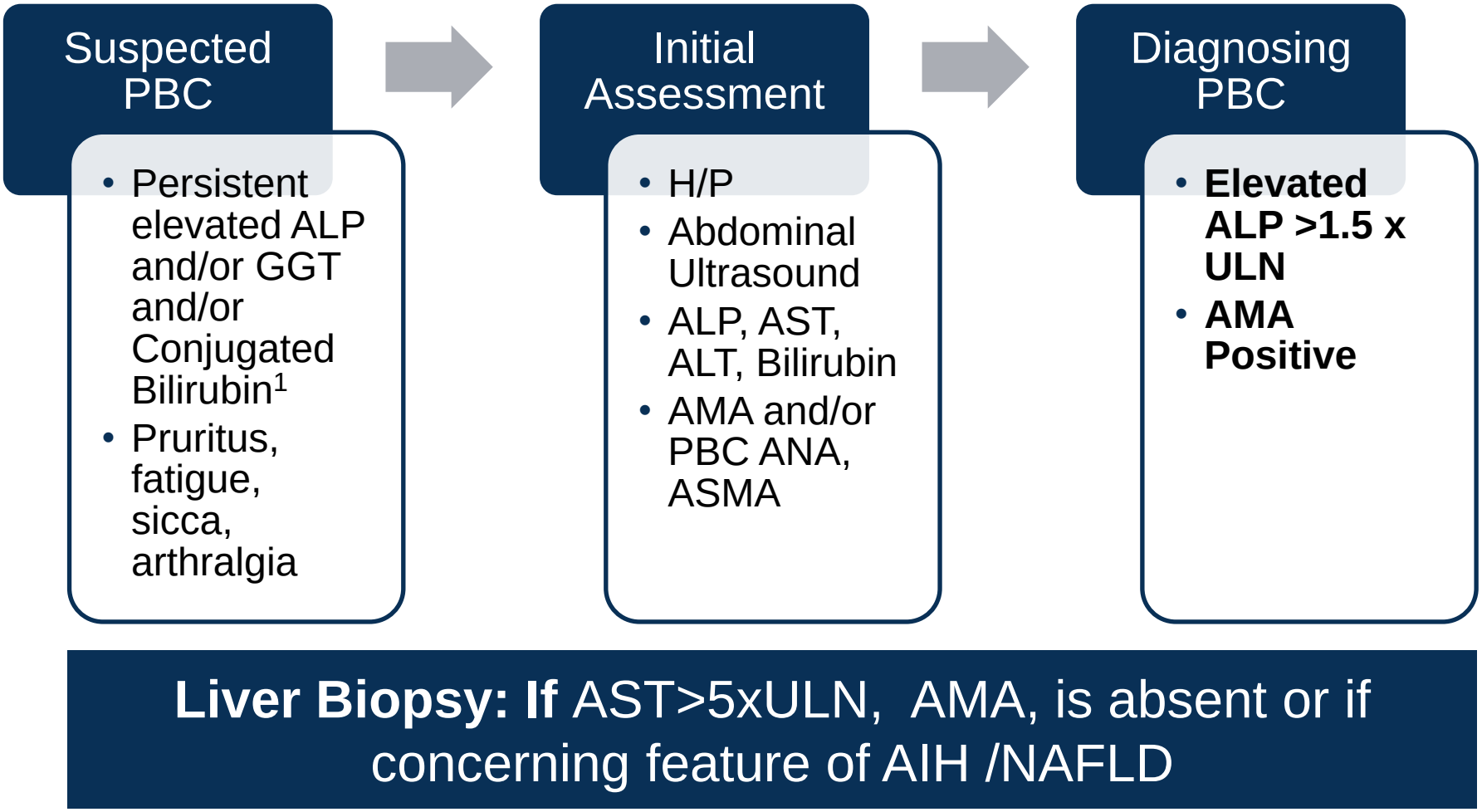
EASL and AASLD Guidelines for PBC



Abbreviations: AIH, autoimmune hepatitis.

1. Hirschfield et al. *Expert Review of Gastroenterology and Hepatolgy*. 2021 Jul 7;1-11. doi: 10.1080/17474124.2021.1945919.

Confirming a PBC Diagnosis According to AASLD



Liver Biopsy: If AST>5xULN, AMA, is absent or if concerning feature of AIH /NAFLD

Abbreviations: alanine aminotransferase; AMA, antimitochondiral antibody; ANA, antinuclear antibody; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT.

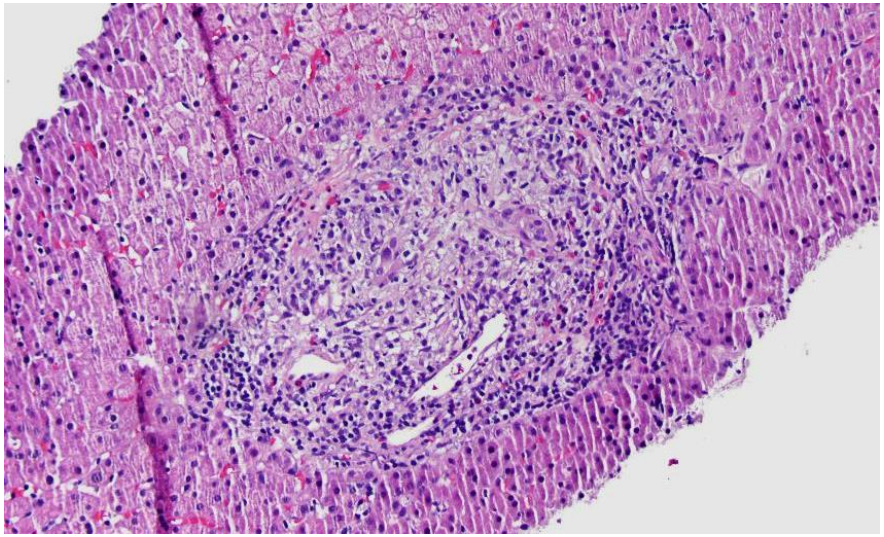
1. Hirschfield et al. *Expert Review of Gastroenterology and Hepatolgy.* 2021 Jul 7;1-11. doi: 10.1080/17474124.2021.1945919.

PBC Diagnostic Criteria

Two out of these 3 criteria are required for the diagnosis of PBC

PBC Diagnosis

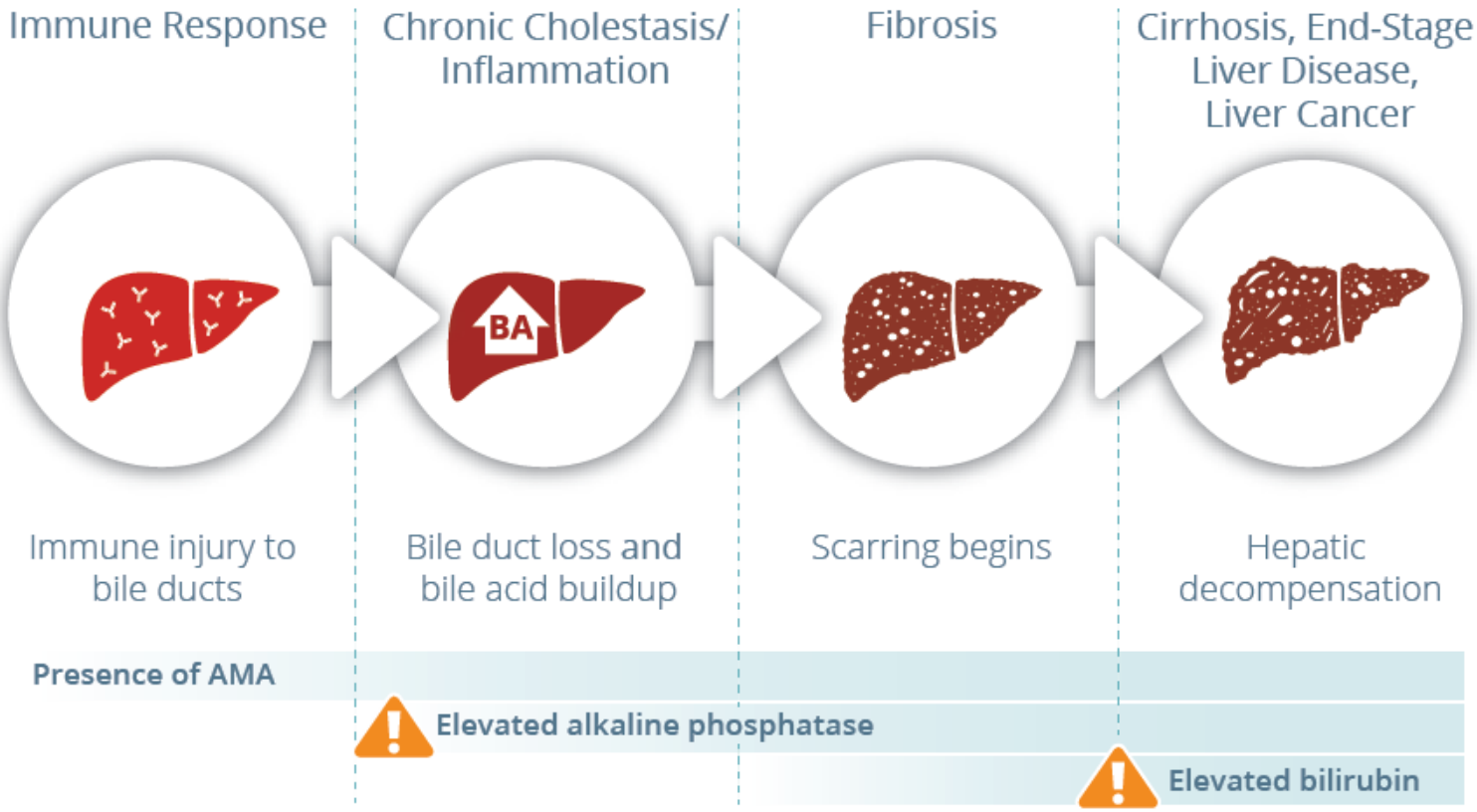
- Unexplained Elevation of ALP ≥ 1.5x ULN
- Positive anti-mitochondrial antibody
- Non-suppurative destructive cholangitis on histology



AASLD 2018.

If Left Inadequately Treated, PBC May Result in Liver Failure, Transplant, or Death[1-3]

Persistent, toxic exposure to bile acid buildup ultimately leads to end-stage disease[1,2,4]



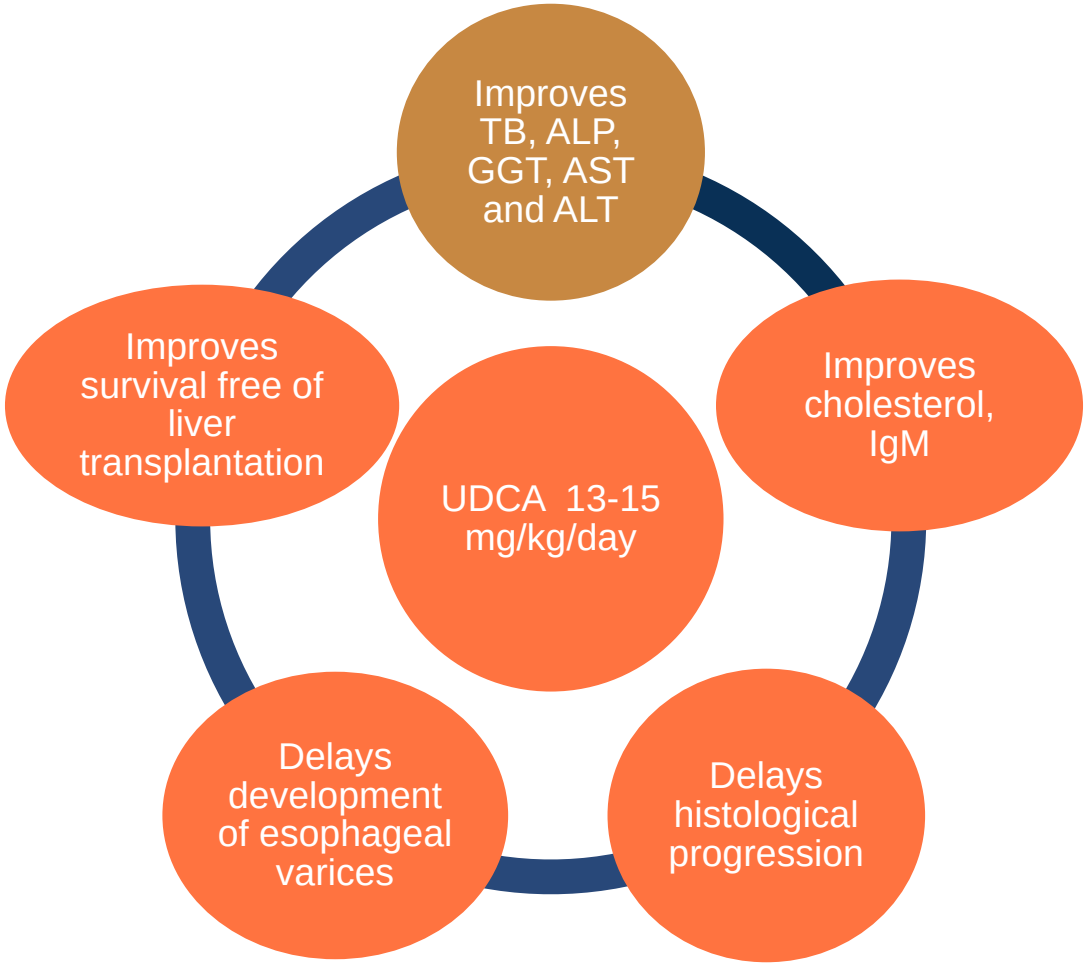
1. Poupon R. *J Hepatol.* 2010;52(5):745-758; 2. Dyson JK et al. *Nat Rev Gastroenterol Hepatol.* 2015;12(3):147-158;
3. Lammers WJ et al. *Gastroenterology*. 2014;147(6):1338-1349; 4. Selmi C et al. *Lancet.* 2011;377(9777):1600-1609.

First Line Therapy: Ursodeoxycholic Acid (UDCA)

- Orally administered, naturally occurring, hydrophilic secondary bile acid
- Dose: 13-15 mg/kg/day
- Improvement in liver tests may be seen within a few weeks and 90% of the improvement usually occurs within 6-9 months[1]
- Adequate response (60%) of patients = similar survival as the standard population[2]

1. Lindor K et al. *Hepatology.* 2009;50:291-308;
2. Reig et al. *The American Journal of Gastroenterology*: June 23, 2021 - Volume - Issue - 10.14309/ajg.0000000000001343.

Therapeutic Effects UDCA

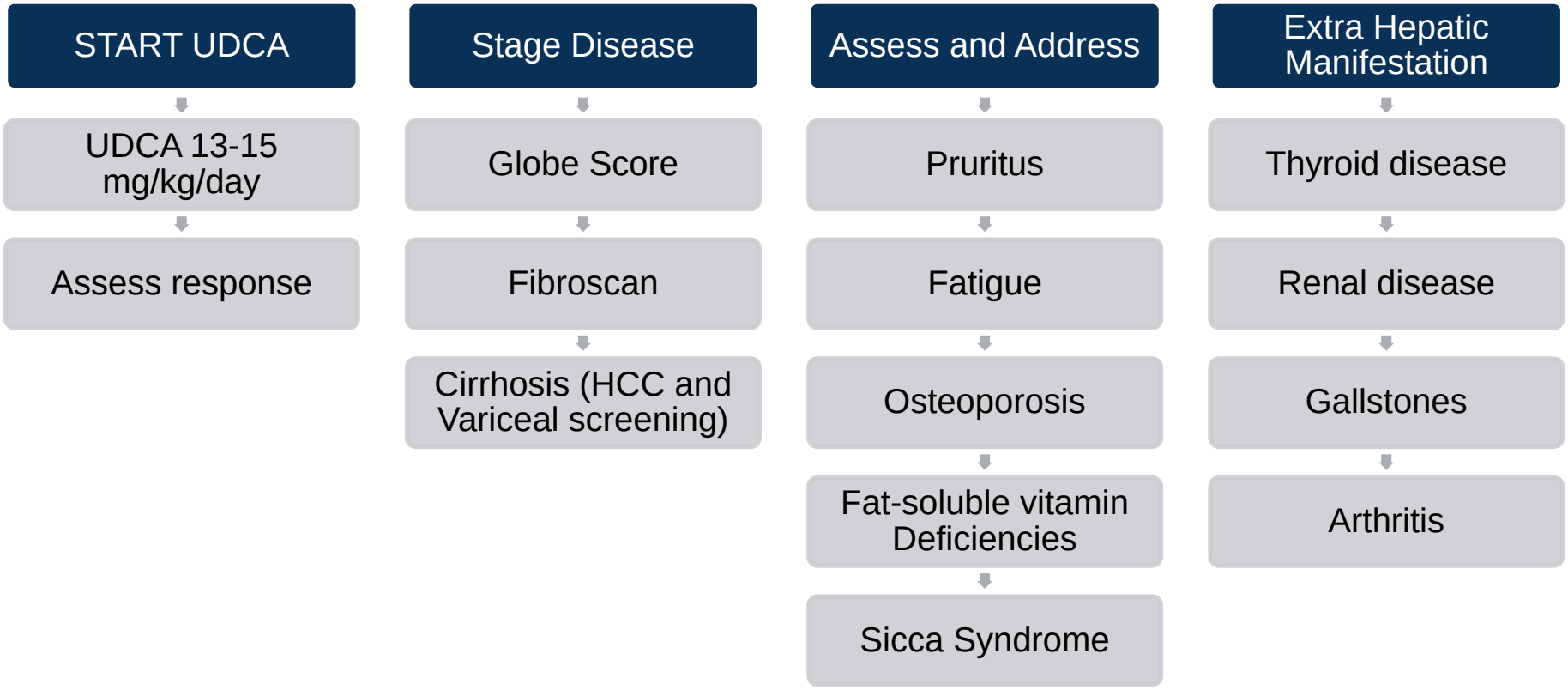


Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; IgM, immunoglobulin M; TB, total bilirubin; UDCA, ursodeoxycholic acid.

Levy C and Lindor KD. In: *Zakim and Boyer's Hepatology: A Textbook of Liver Disease.* Elsevier Inc;2011:738-753.

Graphic courtesy of Dr. Cynthia Levy.

Management of PBC According to AASLD



Response Criteria Models for UDCA

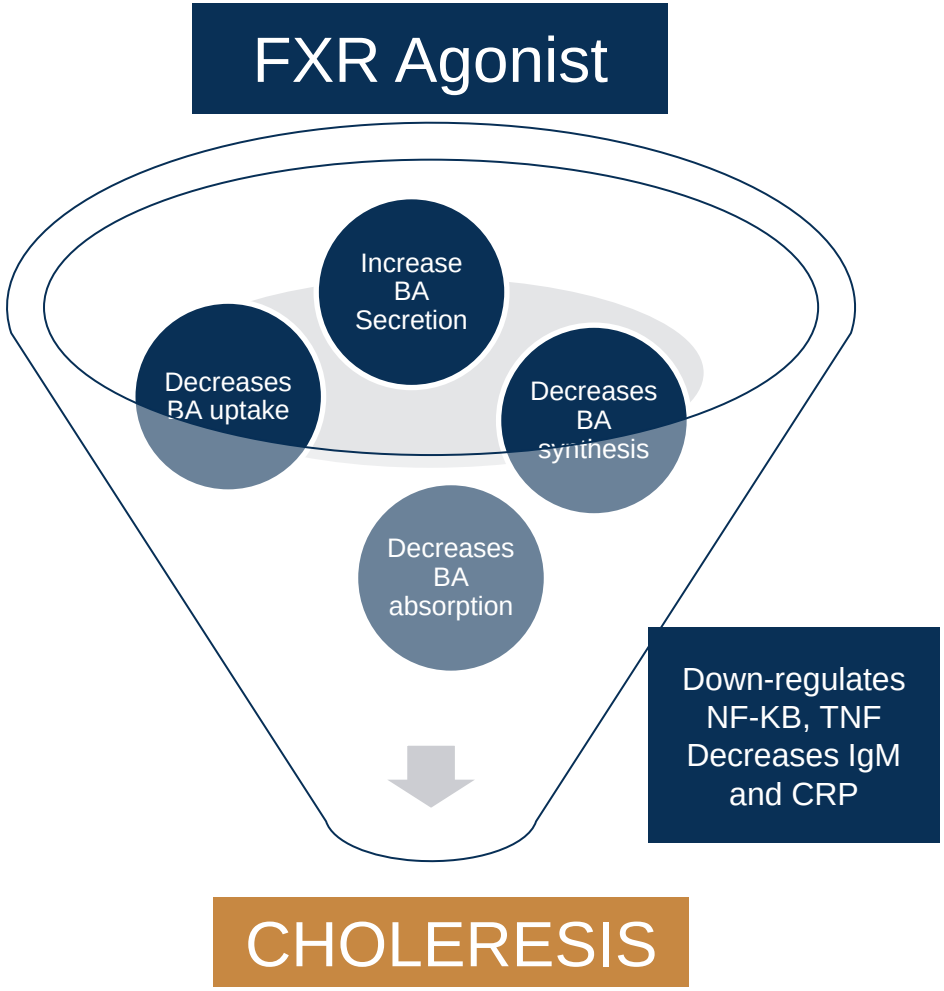
- The Paris-II criteria
  - ALP >1.5x ULN; or
  - AST >1.5x ULN; or
  - Bilirubin >1 mg/dl
- Used to define Adequate response to UDCA

- Globe Score
  - Free online calculator
  - Uses age, total bilirubin, ALP, albumin Platelets

Hirschfield et al. *Expert Review of Gastroenterology and Hepatolgy.* 2021 Jul 7;1-11. doi: 10.1080/17474124.2021.1945919.

Second Line: Obeticholic Acid (OCA)

- In combination with UDCA for patients with PBC who have been treated with UDCA for > 1 year and have incomplete response
- As monotherapy for patients with PBC who are intolerant to UDCA
- Can not be used on Child-Pugh B or C or any patients with prior decompensation episodes, nor patients with any evidence of portal hypertension



Abbreviations: BA, bile acid; NF-KB, nuclear factor kappa beta; TNF, tumor necrosis factor; CRP, C-reactive protein.

Reig et al. *The American Journal of Gastroenterology*: June 23, 2021 - Volume - Issue - 10.14309/ajg.0000000000001343.

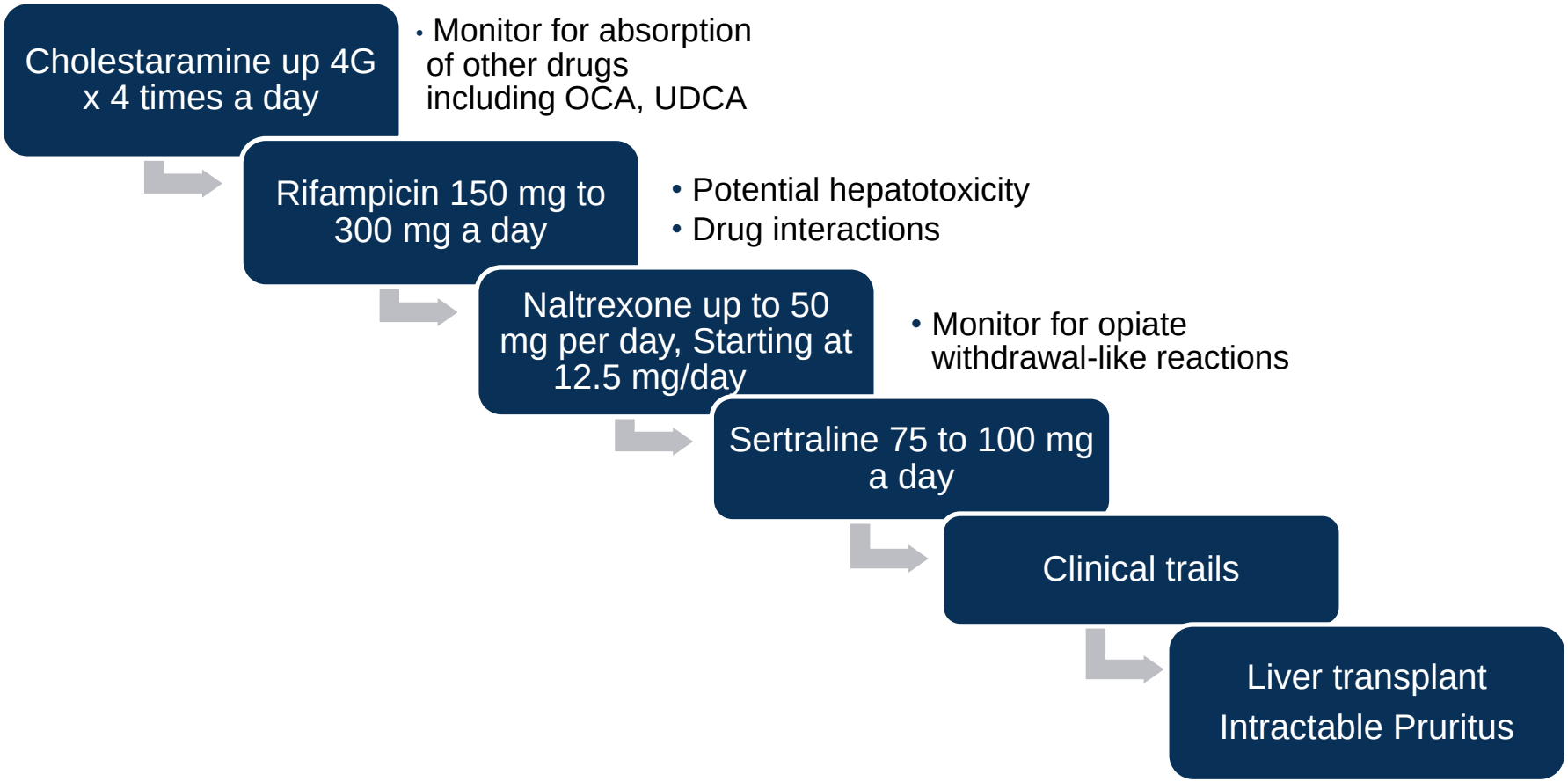
Risk Scarification of PBC Patients on Treatment

Low Risk	Intermediate Risk	High Risk
• Mild elevation in ALP and • Normal bilirubin and • Normal albumin and • Early or no fibrosis	• Age at diagnosis <45 years or • ALP >1.5x ULN or • Abnormal bilirubin or • Low albumin or • Child-Pugh A, Advanced fibrosis/early cirrhosis	• Decompensated cirrhosis (Child-Pugh B or C) or • Compensated cirrhosis with evidence of clinically significant portal hypertension or • Bilirubin >2x ULN; or • Severe pruritus

Tertiary Referral

1. Hirschfield et al. *Expert Review of Gastroenterology and Hepatolgy.* 2021 Jul 7;1-11. doi: 10.1080/17474124.2021.1945919.

Symptom Management: Pruritus



European Association for the Study of the Liver.
Hirschfield et al. *Expert Review of Gastroenterology and Hepatolgy.* 2021 Jul 7;1-11. doi: 10.1080/17474124.2021.1945919.

Symptom Management: Sicca

Dry Mouth (Xerostomia)

- Dental cleaning every 6 months
- Sugar free candy or gum
- Rinse with water
- Saliva substitutes
- Pilocarpine or Cevimeline if refractory to above

Dry Eyes (Keratoconjunctivitis Sicca)

- Artificial tears
- Referral to ophthalmologist
- Pilocarpine or Cevimeline if refractory to artificial tears

AASLD, PBC:2018 Practice Guidelines.

Osteoporosis

AASLD Recommendations

- Dexa Bone Scan every 2 years
- Vitamin D levels yearly and supplement as needed, 1000 IU a day
- Calcium supplementation if osteopenia is present, 1000 to 1500 mg
- If osteoporosis use Alendronate 70 mg once a week
- TSH annually
- If patients become jaundice routine measurement of Vitamin A, D, E and K is recommended to check for deficiencies

AASLD 2018, Practice Guidance.

Fatigue

- No approved treatments
- Assess for other causes such as anemia, depression, sleep disorder, hypothyroidism
- Exercise?
  - Single arm, open label trial to assess the feasibility and efficacy of a home-based exercise program (HBEP) to attenuate fatigue associated with PBC
  - In a preliminary analysis of 25 participants:
  - 23/25 reached the primary endpoint
  - 19/25 reached fatigue scores akin to the control population

HBEP is a safe, feasible, and effective in patients with PBC to attenuate fatigue

Freer et al. AASLD 2020.

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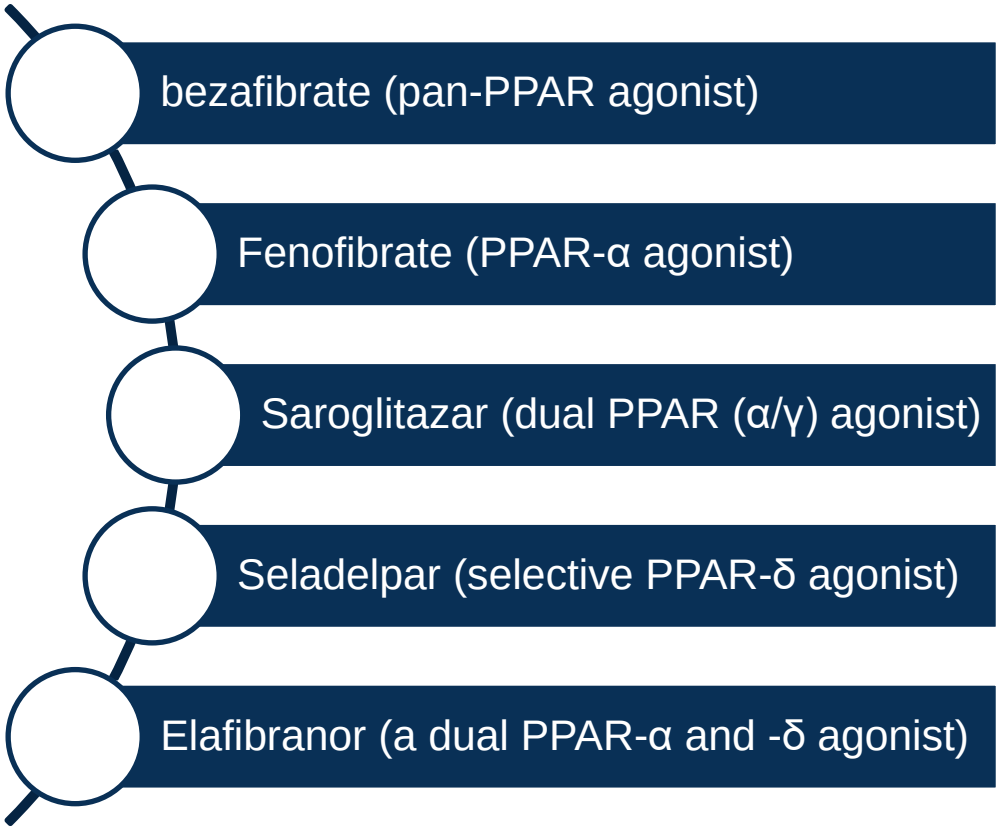
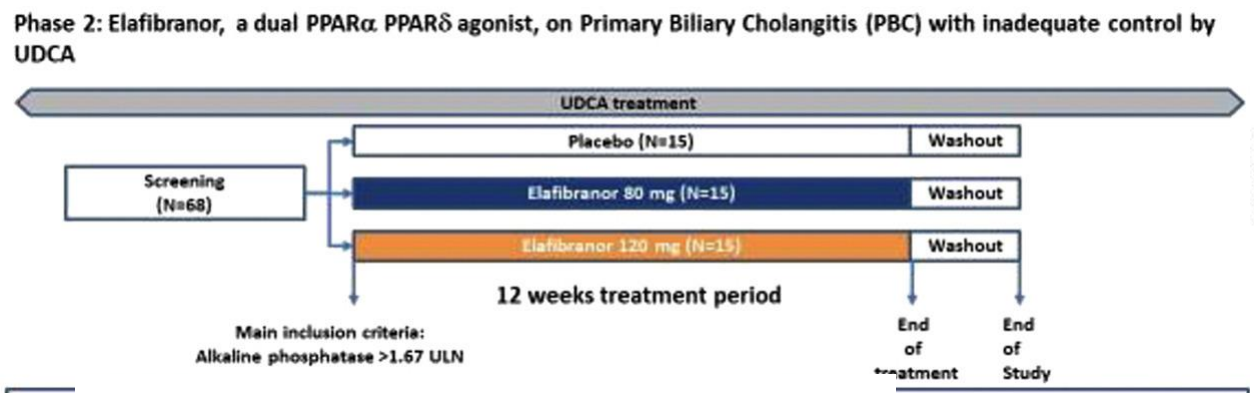
In the Pipeline…

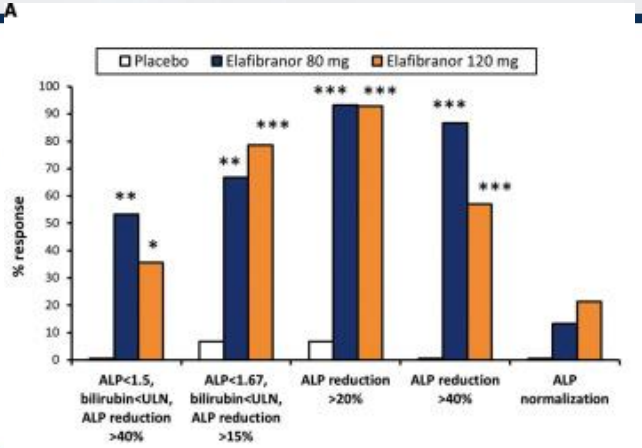
Peroxisome proliferator-activated receptor (PPARs) agonists

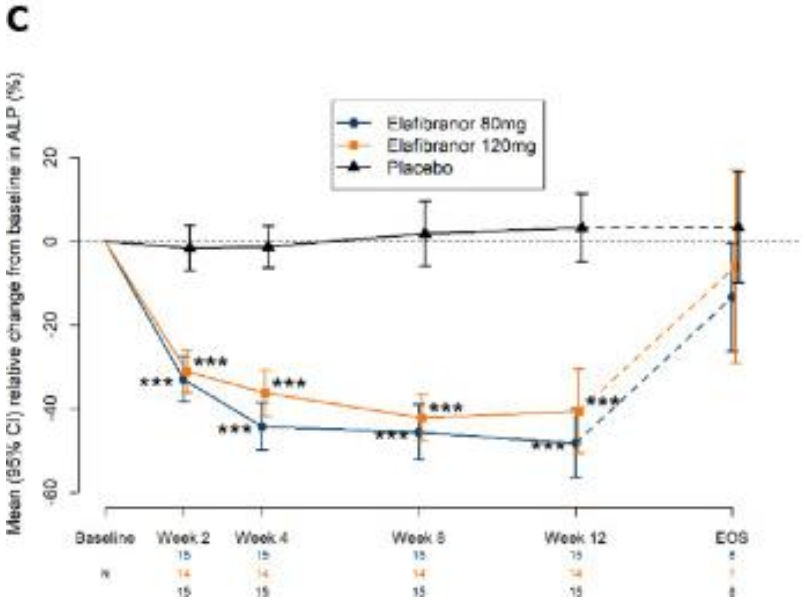
- PPAR are nuclear receptors that occur in three isoforms, α, δ, and γ.
- PPAR's exert in the liver a transcriptional activity regulating many physiologic functions:
  - bile acid homeostasis
  - lipid and glucose metabolism
  - inflammation

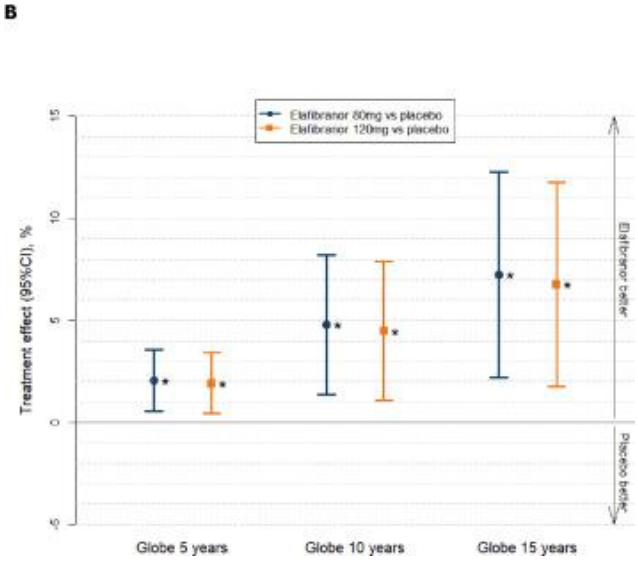


Elafibranor Demonstrates Favorable Efficacy and Safety in Patients With PBC and Incomplete Response to UDCA









Conclusion:
Elafibranor was generally safe and well tolerated.

Significantly reduced levels of ALP, composite endpoints of bilirubin and ALP, as well as other markers of disease activity in patients with PBC and an incomplete response to UDCA.

Slide courtesy of Dr. Cynthia Levy.
Schattenberg et al. *J Hep.* 2021.

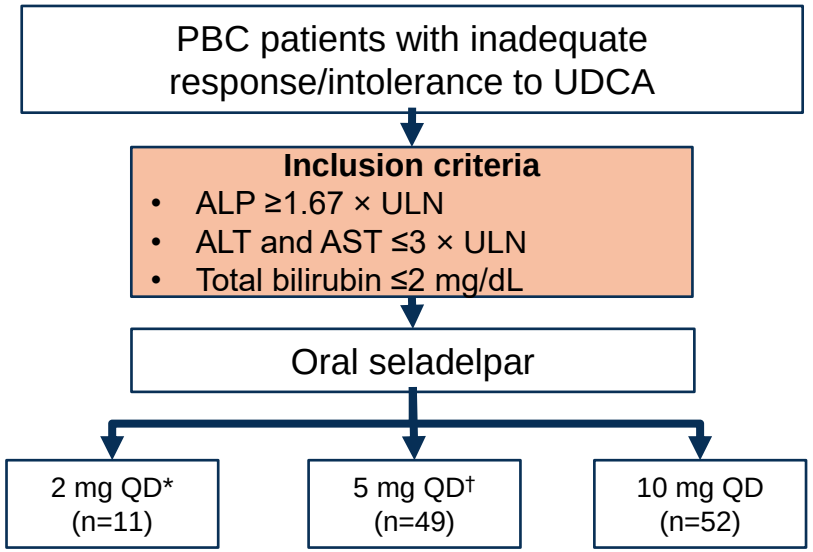
Durability of Treatment Response After 1 Year of Therapy With **Seladelpar** in Patients With PBC: Final Results of an International Phase 2 Study

BACKGROUND & AIMS

- Seladelpar is a potent peroxisome proliferator activated receptor-delta agonist
  - Improved cholestasis markers in PBC
- **AIM**: to evaluate the efficacy, safety, and tolerability of seladelpar during 1 year of treatment in patients with PBC

METHODS

- 1-year, Phase 2, open-label, uncontrolled dose-finding study
- PBC patients with an inadequate response or intolerance to UDCA
- **Primary endpoint**: % change in ALP at 1 year
- **Composite endpoint**: ALP <1.67 × ULN; ≥15% decrease in ALP; total bilirubin ≤ULN



- 112/119 patients evaluated for efficacy
- At 1 year, no patients remained on 2 mg*
- After 1 year, patients could enter a long-term study

Slide courtesy of Dr. Cynthia Levy.
Levy et al. DILC. 2020.

Durability of Treatment Response After 1 Year of Therapy With **Seladelpar** in Patients With PBC: Final Results of an International Phase 2 Study

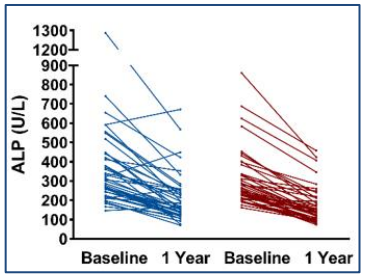
RESULTS

Mean (SD) values	5/10 mg (n=49)	10 mg (n=52)
% female	95.5	
Age, years	57.5 (9)	
Duration of PBC, years	10 (7)	
UDCA dose, mg/kg/day	15 (4)	
Baseline laboratory values		
ALP, U/L	353	301
Total bilirubin, mg/dL	0.76	0.83
GGT, U/L	244	239
ALT, U/L	46	46

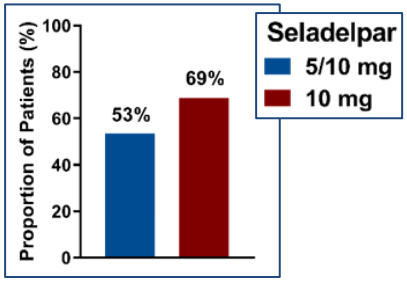
- Seladelpar up to 10 mg appeared safe and well tolerated
- SAEs in 14 patients were unrelated to the drug

After 1 year of treatment

ALP ↓ in nearly all patients



>50% met composite endpoint



Laboratory parameters at 1 year

ALP: ↓ 41% in 5/10 mg and ↓ 45% in 10 mg; total bilirubin: stable; GGT: ↓ 34% in 5/10 mg and ↓ 32% in 10 mg groups;
ALT: ↓ 31% in both groups

- ALP normalized in 14% in 5/10 mg and 33% in 10 mg grps
- 93% with moderate to severe pruritus in the 10 mg grp experienced improvement in itch (VAS decrease ≥20 mm)

CONCLUSION

- Seladelpar resulted in a substantial and sustained biochemical response with a good tolerability and safety profile

Slide courtesy of Dr. Cynthia Levy.
Levy et al. DILC. 2020.

Saroglitazar

- PPAR (α/γ) agonist
- Studied on UDCA unresponsive PBC, Phase 2
- Prospective trial to compare efficacy of 2mg and 4 mg
- Conclusion: Saroglitizar at 2 and 4 mg daily resulted in rapid and sustained improvement in ALP
- The study was terminated because of lack of enrollment

Vuppalanchi R et al. AASLD 2020 Abstract.

Budesonide Add-On Therapy in PBC Patients: Phase 3 trial

- Randomized, double-blind, placebo-controlled trial (Completed)
- 62 patients randomized and treated (ITT population) with 36 months of treatment with UDCA (12–16 mg/kg BW/day) with or without BUD (3 mg tid*)

Improvement in liver histology

- Did not improve histology

Improved liver function

- High drop out rate
- Increased rates of AEs associated with long term steroid use including osteopenia, cataracts and hypertension
- Improvement of liver blood test

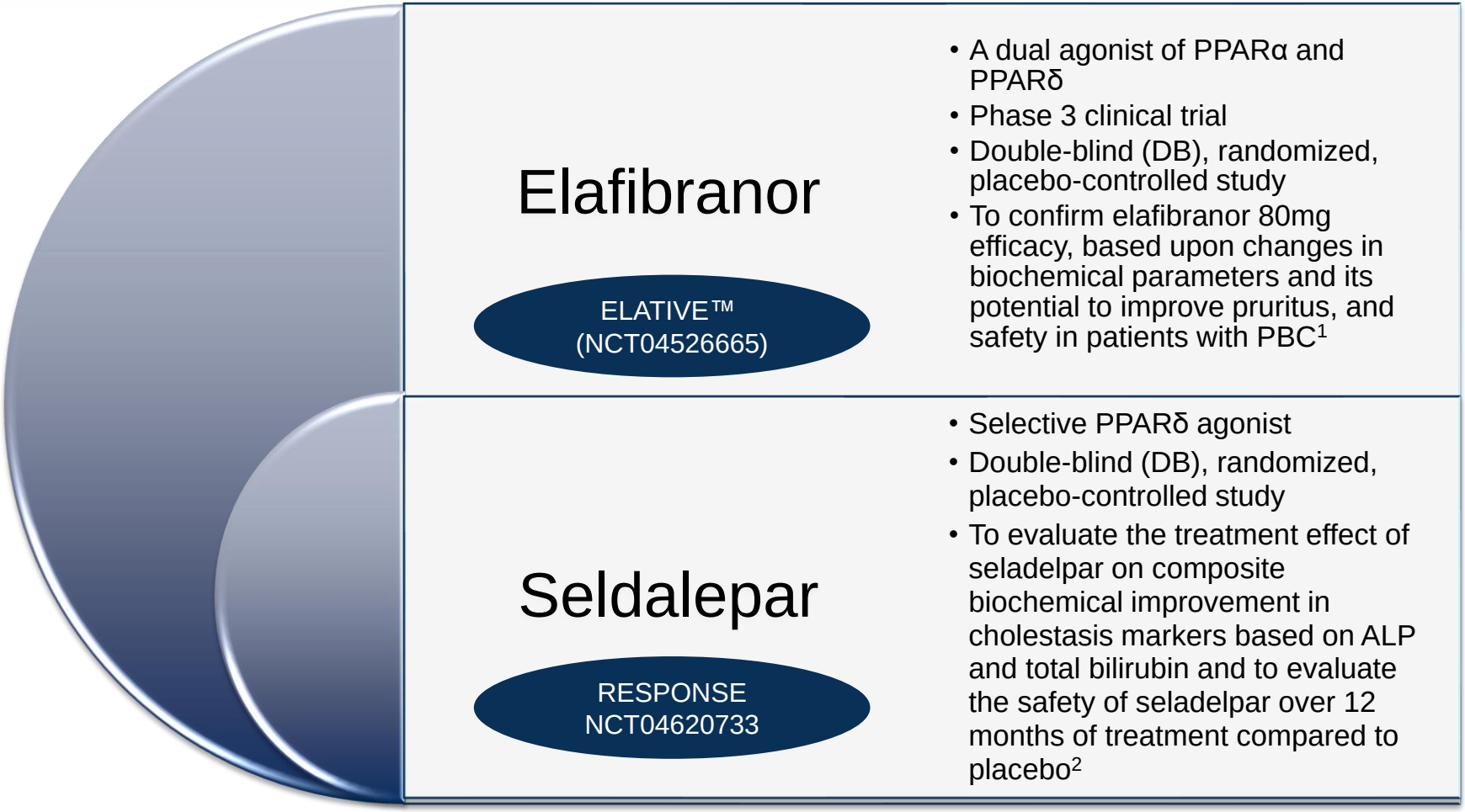
Slide is Courtesy of Dr. Cynthia Levy
Hirschfield G et al. *J Hepatolgy*. 2021.

OCA and Fibrates

- Comparative Effects in a Multicentric Observational Study
  - 86 patients were treated with OCA
  - 250 with fibrates, 81% bezafibrate and 19% fenofibrate
  - 15 with OCA plus fibrates
- **Results**:
  - ALP decrease was higher under fibrates
  - alanine aminotransferase decline was higher under OCA.
  - Adverse events were reported mainly pruritus
  - Discontinuation was more frequent in fenofibrate treatment mainly because of intolerance or adverse events
- **Conclusions**:
  - Second-line therapy with OCA or fibrates improves hepatic biochemistry and the GLOBE score in PBC patients with suboptimal response to UDCA
  - Simultaneous treatment with OCA and fibrates improved ALP as well

Reig et al. The *American Journal of Gastroenterology*: June 23, 2021 - Volume - Issue - 10.14309/ajg.0000000000001343.

Phase 3 Clinical Trials



*Not for liver cirrhosis or history of hepatic decompensation

1. https://clinicaltrials.gov/ct2/show/NCT04526665?cond=elafibranor&draw=2&rank=3;
2. https://clinicaltrials.gov/ct2/show/NCT04620733?cond=NCT04620733&draw=2&rank=1.

Is There a Role for Triple Therapy?

- Retrospective cohort study, 58 eligible patients from 19 centers across seven Western countries
- All patients had failed UDCA or OCA+UDCA or Fibrate therapy +UDCA
- Data suggests that fibrates are more efficient than OCA in reducing ALP level
- OCA could have stronger effects than fibrates on GGT and transaminases
- **Conclusion:** Triple therapy with UDCA, OCA and fibrates has the potential to improve and even normalize the biochemical and clinical features of PBC
- When fibrates were added to OCA and UDCA led to a significant improvement of pruritus

Soret et al. *J Alimentary.* 2021.

Updates since this presentation was created...

HEPATOLOGY

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PRACTICE GUIDELINE

Primary Biliary Cholangitis: 2021 Practice Guidance Update from the American Association for the Study of Liver Diseases

Keith D. Lindor ✉, Christopher L. Bowlus, James Boyer, Cynthia Levy, Marlyn Mayo

First published: 24 August 2021 | https://doi.org/10.1002/hep.32117

Abstract

In May 2021, the FDA issued a new warning restricting the use of obeticholic acid in patients with advanced cirrhosis [1] . This is defined as cirrhosis with current or prior evidence of liver decompensation (e.g., encephalopathy, coagulopathy) or portal hypertension(e.g., ascites, gastroesophageal varices, or persistent thrombocytopenia).

PBC 2021 Update Pending Publication

- **Obeticolic acid:** can not be used in patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event (4) compensated cirrhosis with evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) (4) complete biliary obstruction.
- **Fibrates:** can be considered off label alternative for patients with PBC not responding to UDCA. Discouraged in patients with decompensated disease.

Summary

- PBC Diagnosis can typically be made based on persistent cholestatic liver profile and AMA positivity after other common liver diseases have been excluded
- Risk stratification is important in this patient population
- The use of AASLD/EASL Clinical Practice Guidelines for PBC improves uniform practice
- Is important to assess and manage symptoms of pruritus, sicca, osteoporosis and fatigue
- Promising drugs are in late-stage development