GI Alliance

Advancing GI Patient Care 2021

SATURDAY, JULY 24, 2021

Accredited by:

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This program is supported by an educational grant from
Janssen Biotech, Inc., Mallinckrodt Pharmaceuticals and Pfizer Inc.

Cholestatic Liver Diseases: Best Practices and Emerging Therapies

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Faculty Disclosures

Anil Seetharam MD

- There are no financial disclosures relevant to this topic to disclose.

Outline

- Primary Biliary Cholangitis (PBC)
- Primary Sclerosing Cholangitis (PSC)
- Management
- Emerging Therapies

Primary Biliary Cholangitis

- Chronic nonsuppurative cholangitis affecting interlobular bile ducts
- Middle aged female with elevation in alkaline phosphatase
- Serologic signature: antimitochondrial antibody (AMA)
- Primary symptoms: fatigue and itching
- Associated autoimmune conditions: Sjogren’s, CREST, Raynaud’s

PBC Diagnostics

- AMA Ab usually seals diagnosis
- Liver biopsy rarely needed: “florid duct” lesion
- Portal venules compressed by inflammatory reaction: portal hypertension without significant fibrosis
- “AMA negative PBC” treated the same

PBC Management

- Ursodeoxycholic Acid (UDCA) mainstay of treatment
  - 13 to 15mg/kg
  - Serial ALP monitoring
- 40% of patients do not respond to UDCA
- Obeticholic Acid (OCA)
  - Farnesoid X Receptor (FXR) Agonist
  - Begin at 5mg/day and titrate
  - Avoid in decompensated liver disease

Primary Sclerosing Cholangitis

- Multifocal extrahepatic bile duct strictures
- Strong association with inflammatory bowel disease
- Should be differentiated from IgG4 related cholangiopathy
- “Small-duct” variant

PSC Diagnosis

- MRCP is preferred diagnostic
- Liver biopsy rarely needed; “onion skin” fibrosis
- Dominant Stricture: clinically significant stenosis in the extrahepatic biliary tree
  - <1.5 mm in CBD; <1 mm intrahepatic

PSC Management

- AASLD recommends against use of UDCA in PSC
  - “High dose” not recommended; intermediate doses sometimes considered
- Evaluation and stenting of dominant strictures; antibiotics for cholangitis

PSC Surveillance

- Colorectal cancer
  - Fivefold increased risk compared to IBD with no PSC
- Cholangiocarcinoma
  - Lifetime risk up to 20%
  - Serial MRCP and CA 19-9
  - Suspicious lesions: ERCP for tissue analysis

Cholestatic Disease Management

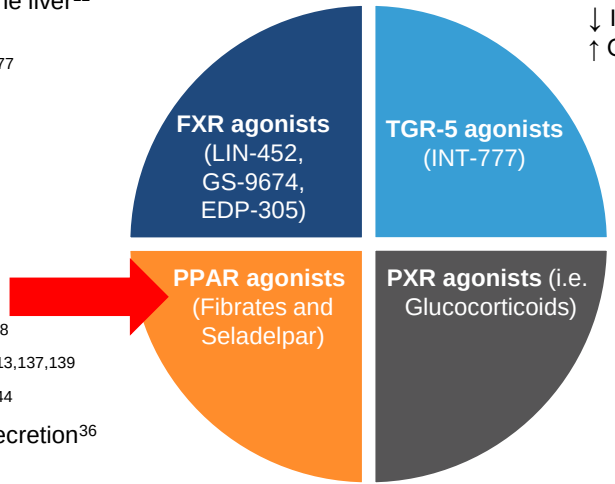
- Pruritis
  - Diverse mechanisms
  - Treatment involves trial and error
    - Lifestyle measures
    - Cholestyramine 4 grams a day titrated up
    - Naltrexone 12.5 mg BID
    - Rifampin
    - SSRIs

Cholestatic Disease Management

- Bone Health
  - Greater risk of osteopenia/osteoporosis
  - Bone mineral density screening every 2 years
  - Calcium and vit D supplementation
- Advanced Fibrosis
  - Transient elastography validated for staging
  - Variceal Screening
  - Biannual HCC screening in cirrhotic
  - Referral to liver transplant center

Emerging Therapies

↓ BA synthesis[75]
↓ BA uptake and ↑ BA secretion out of the liver[11,12]
↓ BA uptake and ↑ BA secretion out of the gut[12]
↑ Conjugation of BA in the liver[12]
↑ Detoxification of BA[12]
↑ Bicarbonate secretion[77]
↓ Inflammation[12]
↓ Gluconeogenesis[32]
↑ Glycogen synthesis[32]
↑ Lipogenesis[32]
↑ Liver regeneration[136]



↑ Bicarbonate secretion[77]
↑ Insulin sensitivity/secretion(via GLP-1)[75]
↑ Energy expenditure (via iodothyronine deiodinase)[75]
↓ Inflammation[11,16]
↑ Gallbladder relaxation[75]

↓ BA production[113,137,138]
↑ Detoxification of BA[1113,137,139]
↓ BA uptake in the liver[44]
↑ Biliary phospholipid secretion[36]
↑ Fatty acid oxidation[16]
↓ Inflammation[44,46]
↑ Improve insulin sensitivity[131]
↑ BA uptake in the intestines[140]

↑ Detoxification of BA[75]
↓ BA production[66]
↑ BA secretion out of the liver[141]
↓ Inflammation[142]
↓ Gluconeogenesis[142]
↑ Lipogenesis[142]

Goldstein et al. *Liver International*. 2018;38:1520–1535.

Fibrates

- FDA Approved for lipid-lowering
- Activate PPARα
- Open-label study: PBC subjects with an ALP> twice ULN after UDCA treatment treated with fenofibrate 160 mg/ day for 48 weeks
  - Serum ALP decreased by approximately 50% at the end of the study period
- Side effects: heartburn, myalgias, rise in aminotransferases

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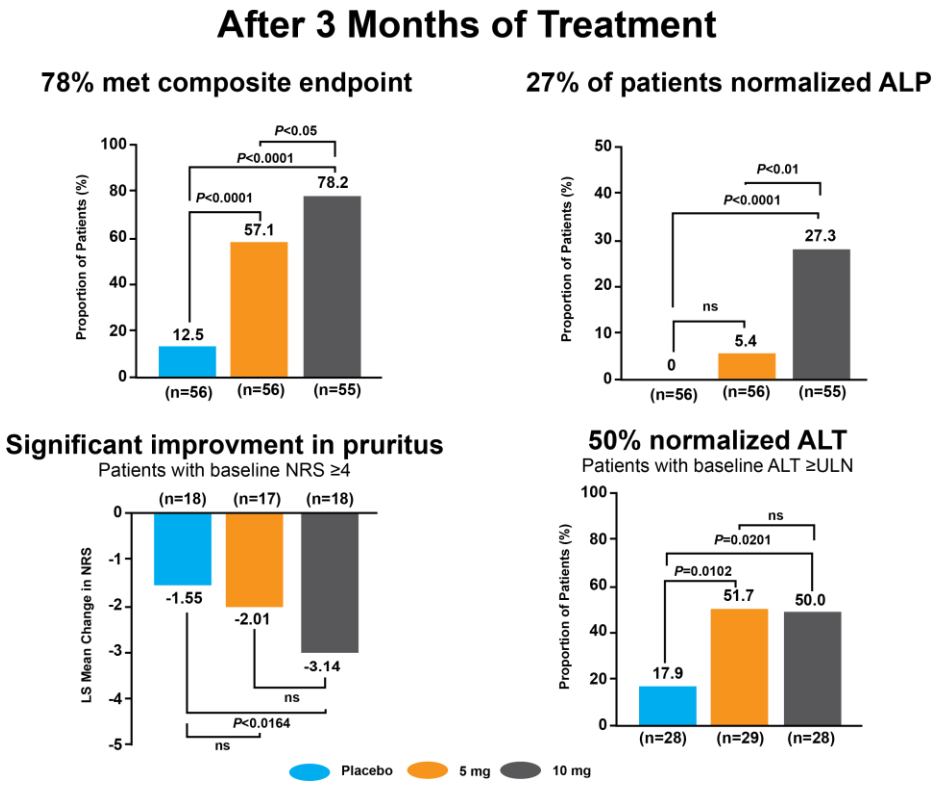

Accessed Liver Learning. *AASLD.* 2020; Hirschfield GM et al. Abstract LO11.

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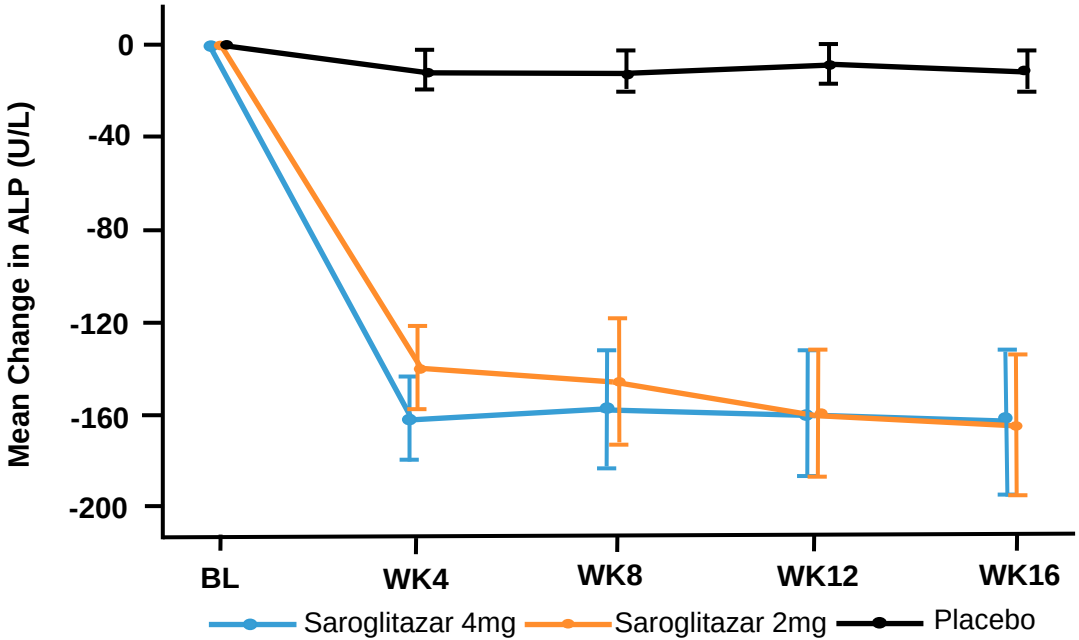

Accessed Liver Learning. *AASLD*. 2020; Vuppalanchi R et al. Abstract LO12.

Summary

- Cholestatic disorders impair liver function and quality of life
- Liver biopsy rarely needed
- Management of pruritis is trial and error
- Cancer screening critical in PSC
- Medical therapy remains an unmet need, but armamentarium is growing