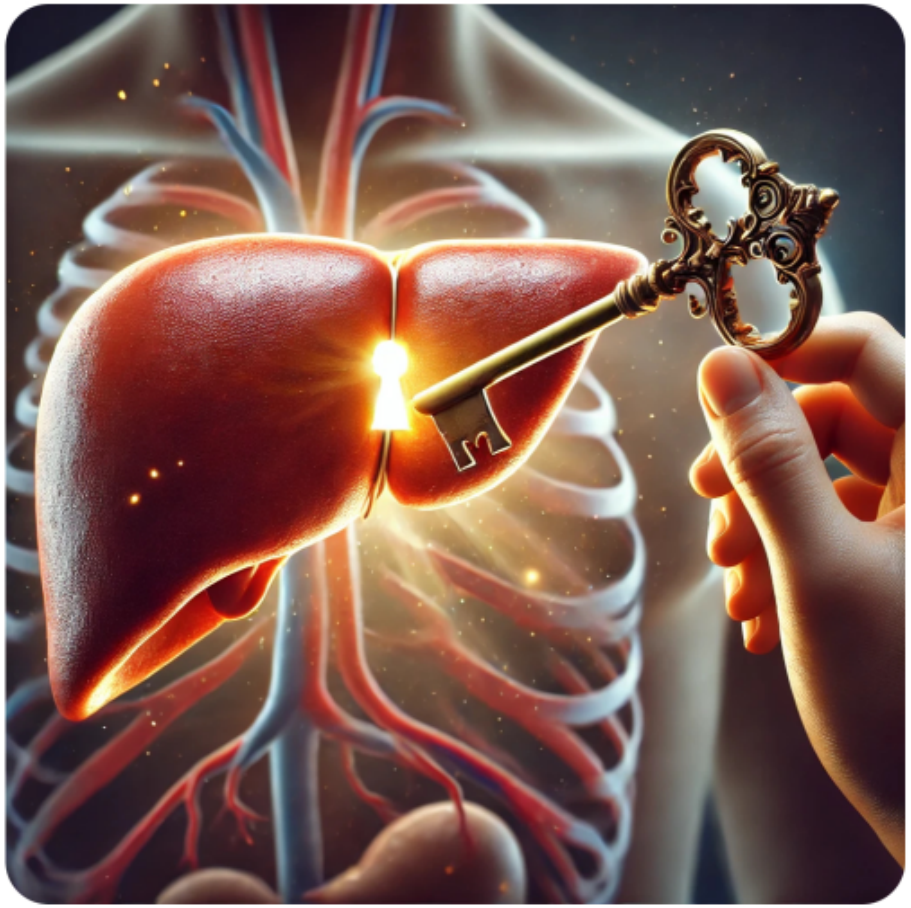

Unlocking the Liver:

Decoding Autoimmune Liver Diseases

- Autoimmune Hepatitis (AIH)
- Primary Biliary Cholangitis (PBC)
- Immune-Mediated Liver Injury from Checkpoint Inhibitors (ILICI)

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UNIVERSITY OF CALGARY
CUMMING SCHOOL OF MEDICINE

WGO

Train the Trainers

ACG 2025
October 24-29, Phoenix, AZ

Talk Objective

- Describe the diagnosis and management of AIH, PBC and ILICI

- **Disclaimer:** I will be speaking on the off-label use of
  - bezafibrate for PBC
  - mycophenolate mofetil and rituximab for AIH

Learning Outcomes

By the end of this talk, you will be able to change your practice by:

1) recognizing the role of liver biopsy in autoimmune conditions
2) selecting first and second line agents for patients with AIH and PBC
3) managing patients with liver injury related to checkpoint inhibitors

CHAPTERS

I. **Autoimmune Hepatitis**

II. Primary Biliary Cholangitis

III. Immune-mediated Injury from Checkpoint Inhibitors

First presentation

- 35-year-old physiotherapist has abnormal liver tests
- Mild fatigue, arthralgias and recently noticed jaundice
- Previously healthy, non drinker, no illicit drug use
- No prescribed, over-the-counter or herbal medications
- Twin sister has Grave's disease, but no family history of liver disease
- Exam – Vitals normal, BMI 23, unremarkable other than mild scleral icterus, no stigmata of cirrhosis

Investigations

- **ALT 450** (≤ 35 U/L), **AST 395** (≤ 35 U/L), ALP 80 (36-92 U/L), **GGT 120** (≤ 30 U/L)
- **bilirubin 3.6** (0.3-1.2 mg/dL), **albumin 30** (3.5-5.5 d/dL), INR 1.0
- CBC, electrolytes, creatinine, glucose, HBA1c, lipids normal
- HBsAg negative, anti-HCV antibody negative
- Transferrin saturation, A1AT level, ceruloplasmin normal
- ANA negative, **ASMA positive 1:160**, AMA negative
- IgA 100 (70-300 mg/dL), **IgG 3000** (640-1430 mg/dL), IgM 50 (20-140 mg/dL)
- Abdominal US = unremarkable, no biliary dilatation
- Transient elastography = median liver stiffness **15 kPA**, CAP 180

Questions

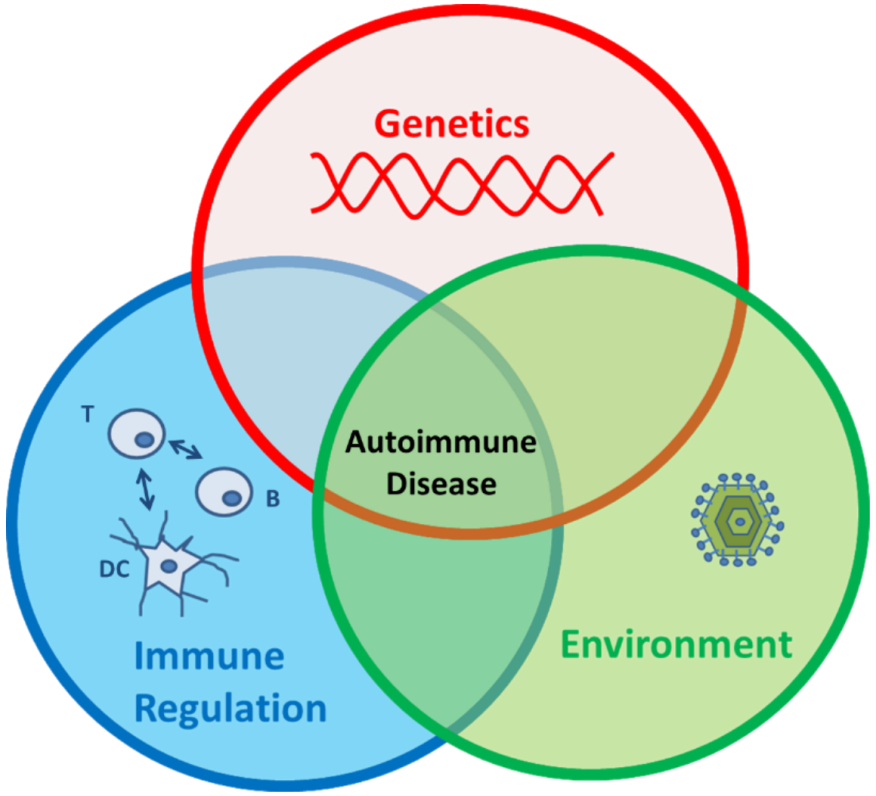
1) What is the most likely diagnosis?

2) Does she require a liver biopsy?

3) How would you manage her liver disease?

Autoimmune Hepatitis

- Prevalence
  - 31 per 100,000 in USA
- More common in women (4:1)
- All ages
  - More common in elderly
- All ethnic groups
  - More common in Caucasians



Minocycline
Nitrofurantoin
Phenytoin
Trazodone
Propylthiouracil
Isoniazid
Sulfonamides

Presentations

- Asymptomatic rise in liver tests
  - mild or moderate ALT
  - often other autoimmune diseases
  - frequently have cirrhosis at diagnosis
- Symptomatic
  - fatigue, arthralgias, jaundice
  - complications of cirrhosis
- Severe acute hepatitis (40%)
  - ALT > 1000, jaundice, coagulopathy

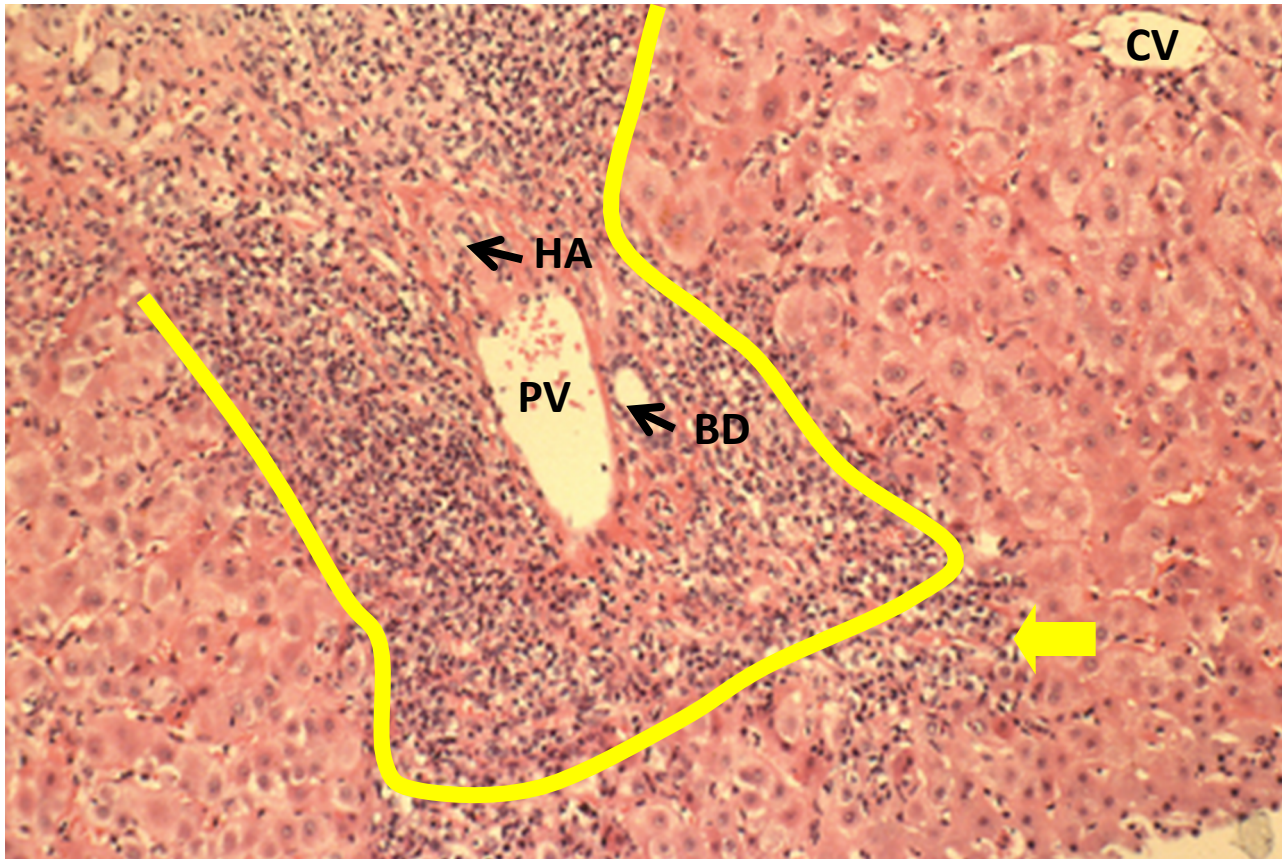
Autoantibodies

- Anti-nuclear antibody (ANA) in 67%
- Anti-smooth muscle antibody (ASMA) in 87%
- Anti-liver kidney microsomal (anti-LKM)
- Not specific for AIH
- Not pathogenic in AIH
  - epiphenomena of liver damage & immune activation
- Poor correlation with course and can fluctuate

Liver biopsy needed for diagnosis!

Adapted from Manns MP, et al. Hepatology 2010; 51(6): 2193-213.

Histology



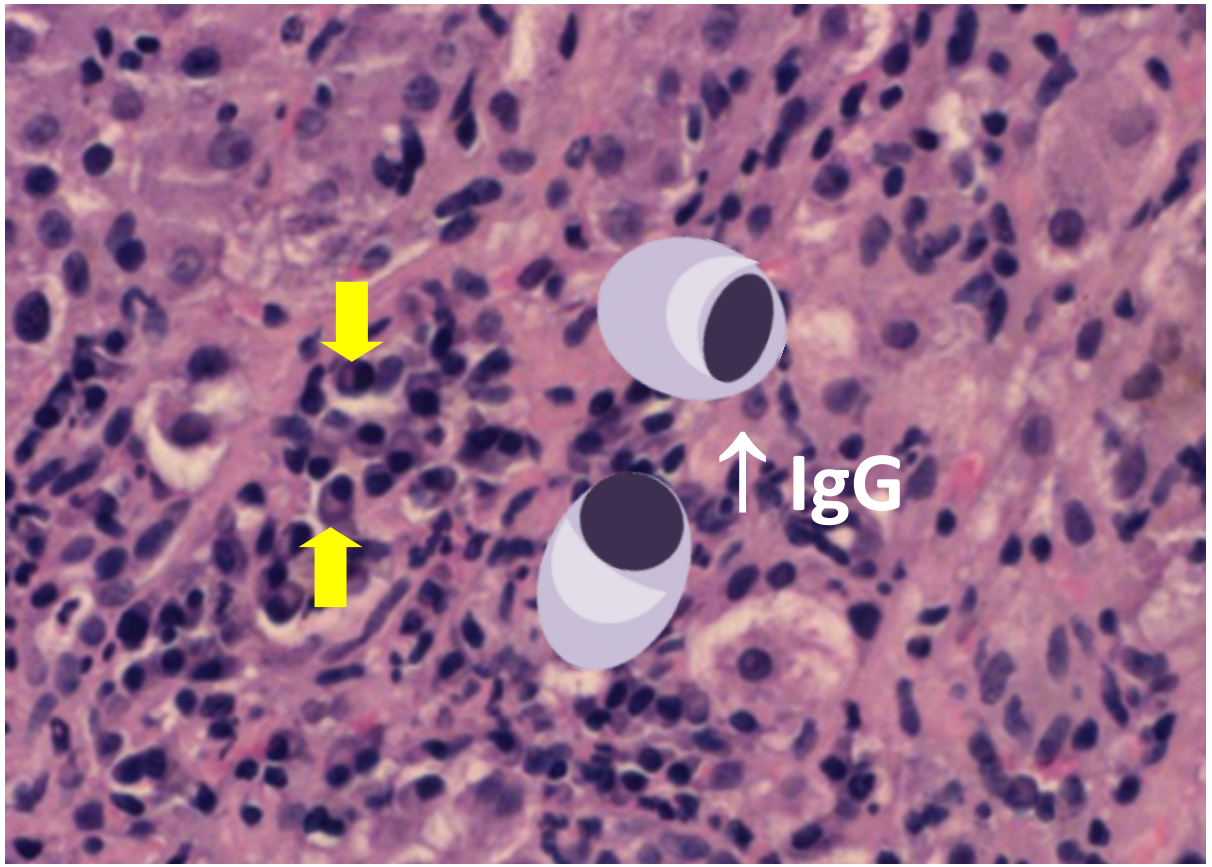


Image Source: http://www.aasld.org/practiceguidelines/Documents/AIH2010.pdf

Up to 1/3 of AIH now have coexisting MASLD

Mack CL, et al. 2019 AASLD guidelines. Hepatology 2020; 72(2): 671-722.

Natural History

- Delay in diagnosis harmful
  - 40% severe AIH dead within 6 mo
  - 40% develop cirrhosis
- Treatment saves lives
  - 20-yr survival > 80% (= controls)
- Controllable, not curable
  - cyclical remissions and flares

Absolute Indications

- **AST ≥ 10 x ULN**
- **AST ≥ 5 x ULN and γ globulin ≥ 2 x ULN**
- **interface hepatitis**
- **severe symptoms**

Manns MP, et al. Hepatology 2010; 51(6): 2193-213.

Treatment

TMPT

Week	Prednisone (mg/d)	Combination	
		Prednisone (mg/d)	Azathioprine (mg/d)
1	60	30	50
2	40	20	50
3	30	15	50
4	30	15	50
Until Remission	20	10	50

Budesonide also 1st line

- **Avoid if cirrhosis or acute severe AIH**

Manns MP, et al. Hepatology 2010; 51(6): 2193-213.

Mack CL, et al. Hepatology 2020; 72(2): 671-722.

Side-effects

Prednisone

- Face rounding
- Dorsal hump
- Striae
- Hirsutism
- Alopecia
- Wt gain

80% @ 2yrs

- Emotional liability
- Psychosis
- Diabetes
- Cataracts
- Osteopenia
- Hypertension

13% stop early

Azathioprine

- ↓ WBC
- ↓ platelets

46% (if cirrhosis)
6% stop early

- N/V
- Rash
- Arthralgias
- Fever

5%

- Cancer risk

3% @ 10yrs

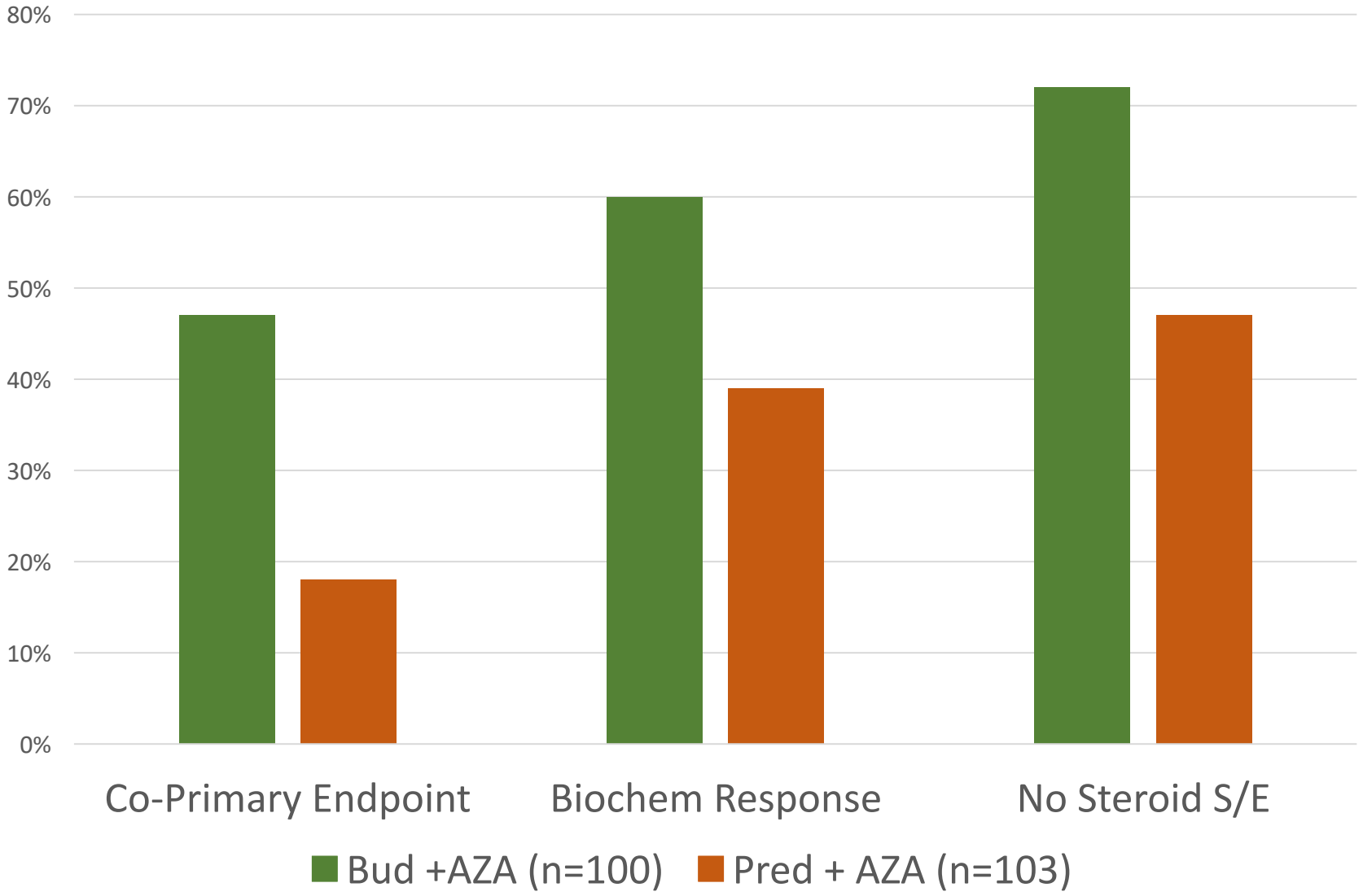
US database – 2203 AIH patients

- 81% single regime for > 6 mo during 1st 2 years
  - 52% AZA alone
  - 17% AZA / Pred
  - 13% Pred alone
  - 2% Budesonide combo
  - 2% Budesonide alone

Bittermann T, et al. Hepatology 2025; 81(2): 423-435.

Manns MP, et al. Hepatology 2010; 51(6): 2193-213.

Budesonide RCT



Manns MP, et al. Gastroenterology 2010; 139: 1198–1206.

Budesonide as 1st line treatment in patients with AIH seems inferior to standard predni(so)lone administration

Study Population

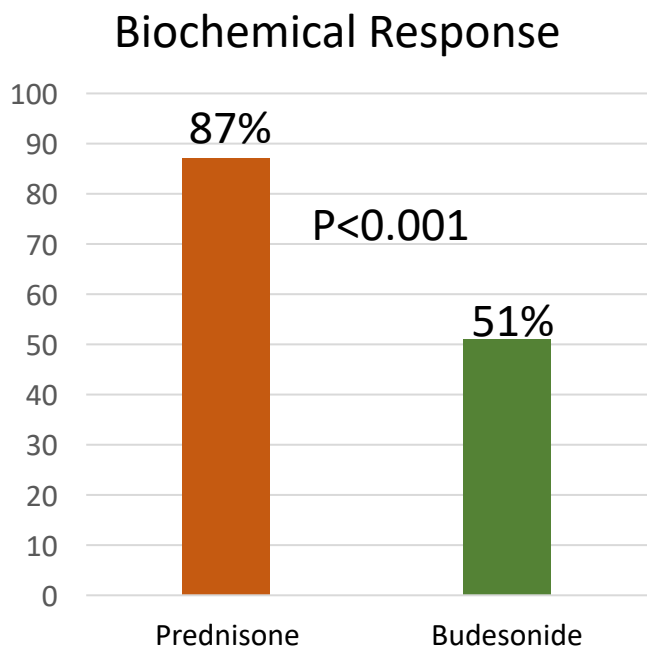
21 centers in Spain
597 patients
151 on budesonide

381 in main analysis
- No cirrhosis
- No acute / severe
- With AZA

276 prednisone

105 budesonide

Outcomes



Conclusions

a) Use of budesonide as 1st line treatment is low

b) Prescribed to patients with less disease activity

c) **Budesonide was inferior** to prednisone as 1st line drug

Diaz-Gonzalez A, et al. Hepatology 2023; 77(4): 1095-1105.

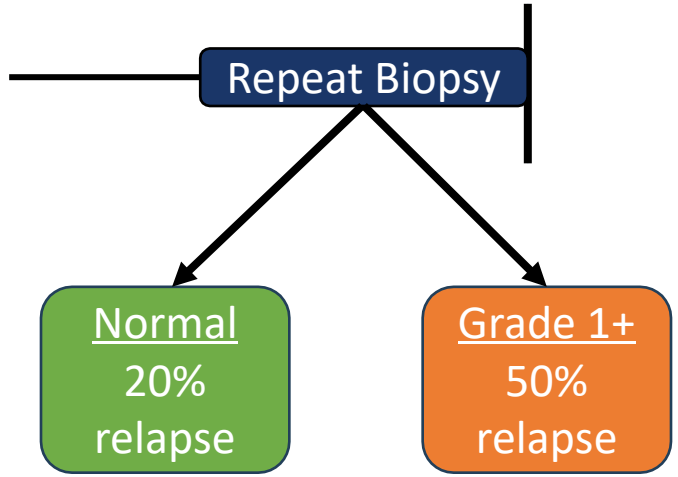
EDITORIAL

Treatment of autoimmune hepatitis: Budesonide does not solve our problems

Steinmann S, Lohse AW. Hepatology 2023; 77(4): 1071-73.

Remission

- Biochemical = normal ALT and IgG
- Histological = no or minimal inflammation on biopsy (often lags)
- Remission rare in first 12 months
  - average at least 2 years of treatment
- Liver biopsy done prior to stopping meds
  - half with normal ALT have interface hepatitis
- Management upon remission
  - withdraw prednisone and then stop AZA
  - regular monitoring for relapse



Refractory AIH

- Worsening clinical, biochemical & histology despite compliance
- 1st line
  - prednisone 60 mg or prednisone 30 mg and AZA 150 mg[1]
- 2nd line
  - **mycophenolate mofetil[2]**
  - tacrolimus, budesonide, methotrexate, cyclosporine, cyclophosphamide
  - rituximab[3]

[1]Manns MP, et al. Hepatology 2010; 51(6): 2193-213.

[2]Mack CL, et al. Hepatology 2020; 72(2): 671-722.

[3]Burak KW, et al. Can J Gastroenterol 2013; 27(5): 273-280.

Follow Up

1) **What is the most likely diagnosis?**
   - **AIH**

2) **Does Amber require a liver biopsy?**
   - **YES** = consistent with AIH (Grade 3, Stage 3-4)

3) **How would you manage her liver disease?**
   - **Prednisone** 60 mg -> 30 mg + **AZA** 50 mg daily (after TMPT)

   - After one year ALT 30 (<35 U/L), **IgG 1500** (640-1430 mg/dL)
   - Steroids stopped due to weight gain
   - Maintained on AZA 50 mg daily

CHAPTERS

I. Autoimmune Hepatitis

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2 years later

- Returns with increasing liver tests and increasing fatigue and pruritus
- Azathioprine 50 mg daily, started oral contraceptive pill
- Exam unchanged other than **BMI 27**, no features of decompensation
- **ALT 40** (≤ 35 U/L), **AST 55** (≤ 35 U/L), **ALP 270** (36-92 U/L), **GGT 330** (≤ 30 U/L)
- bilirubin 1.0 (0.3-1.2 mg/dL), albumin 3.5 (3.5-5.5 d/dL), INR 1.0
- ANA negative, **ASMA positive 1:80**, **AMA positive 1:160**
- IgA 100 (70-300 mg/dL), **IgG 1800** (640-1430 mg/dL), **IgM 300** (20-140 mg/dL)
- HbA1c 5.0%, Total cholesterol, LDL, HDL, **TG elevated**
- Abdominal US = unremarkable, no biliary dilatation
- Transient elastography = median liver stiffness **15 kPA**, CAP **300**

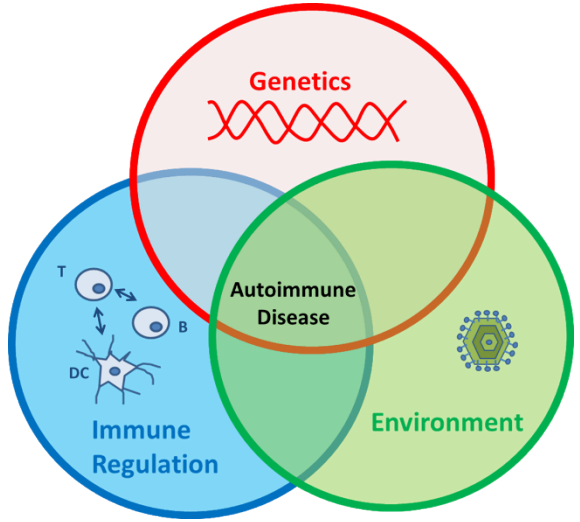
Questions

1) What is the most likely diagnosis?

2) Does she require a repeat liver biopsy?

3) How would you manage her liver disease?

Primary Biliary Cholangitis



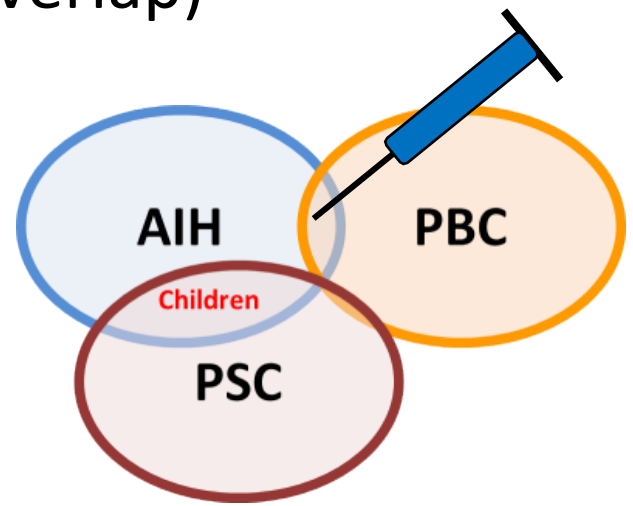
- Female : male = 9:1
- Median age of onset = 50-60 years
- Prevalence
  - 10.0 → 22.7 per 100,000 in Alberta, Canada[1]
  - 21.7 → 39.2 per 100,000 in USA[2]
- Other autoimmune conditions
  - thyroid disease, scleroderma, CREST, Raynaud's

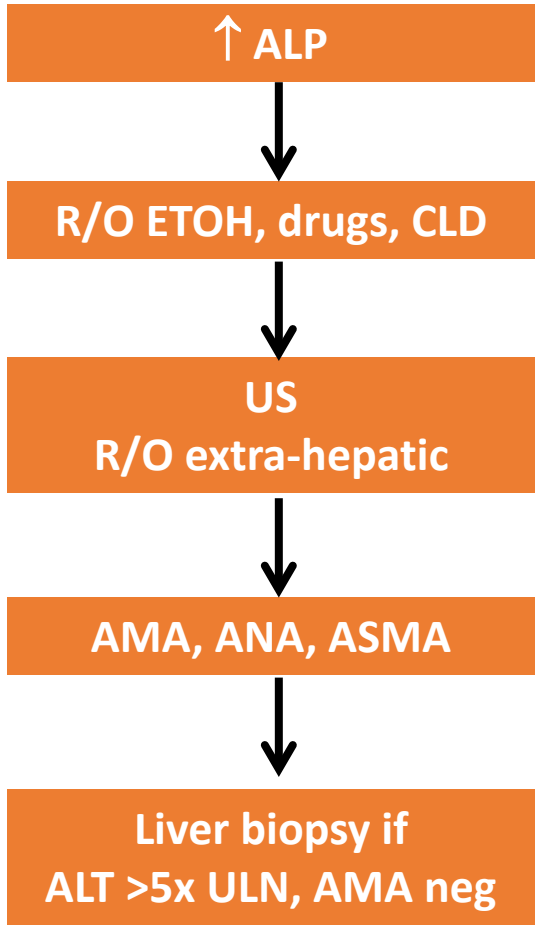
1:1000 women over age 40 in North America

[1] Myers RP, et al. Hepatology 2009; 50(6): 1884-92.
[2]Lu M. Clin Gastroenterol Hepatol 2018; 16(8): 1342-1350.

Diagnosis

- Anti-mitochondrial antibody (AMA)
  - present in 95% (**diagnostic**)
  - pyruvate dehydrogenase complex (PDC-E2)
- ↑ IgM and ↑ cholesterol
  - ↑ ALT and ↑ IgG (? AIH overlap)
- Liver biopsy **only if**:
  - atypical features
  - suspect AMA negative
  - suspect overlap





Adapted from Lindor KD, et al. Hepatology 2009; 50(1): 291-308.

Natural History

- Shorter survival than controls
- 10-year survival of 50-70%
- Median survival 5-8 years if symptomatic
- Poor predictors
  - older age
  - ↑ fibrosis
  - ↑ bilirubin
  - **ALP does not normalize on UDCA**

Mayo Risk Score

- Age
- Bilirubin
- Albumin
- INR
- Edema
- Diuretics

Treatment

- UDCA 13-15 mg/kg once daily
  - separate from cholestyramine by >2 hrs
- Has been shown to:
  - slow histologic progression
  - improve survival free of LT
  - reduces formation of varices
- Minimal impact on symptoms
- Diarrhea and weight gain

60% normalize ALP
- **better natural history**

40% UDCA non-responders
- **ALP >1.67 x ULN or ↑ bili**
  - **obeticholic acid**
  - **PPAR agonists**

Younossi ZM, et al. Am J Gastroenterol 2019; 114(1): 48-63.

Follow Up

1) **What is the most likely diagnosis?**
   - **AIH / MASLD / DILI / PBC overlap**

2) **Does she require a repeat liver biopsy?**
   - **YES** = florid duct lesions, portal inflammation, and cirrhosis, consistent with PBC-AIH overlap

3) **How would you manage her liver disease?**
   - **UDCA** 15 mg/kg daily added to AZA
   - **Cholestyramine** and **sedating antihistamines**

1 year later

- Doing relatively well and no decompensation
- Pruritus improved but still keeps her awake at night
- ALT 25 (≤ 35 U/L), AST 35 (≤ 35 U/L)
- **ALP 185** (36-92 U/L), **GGT 200** (≤ 30 U/L)

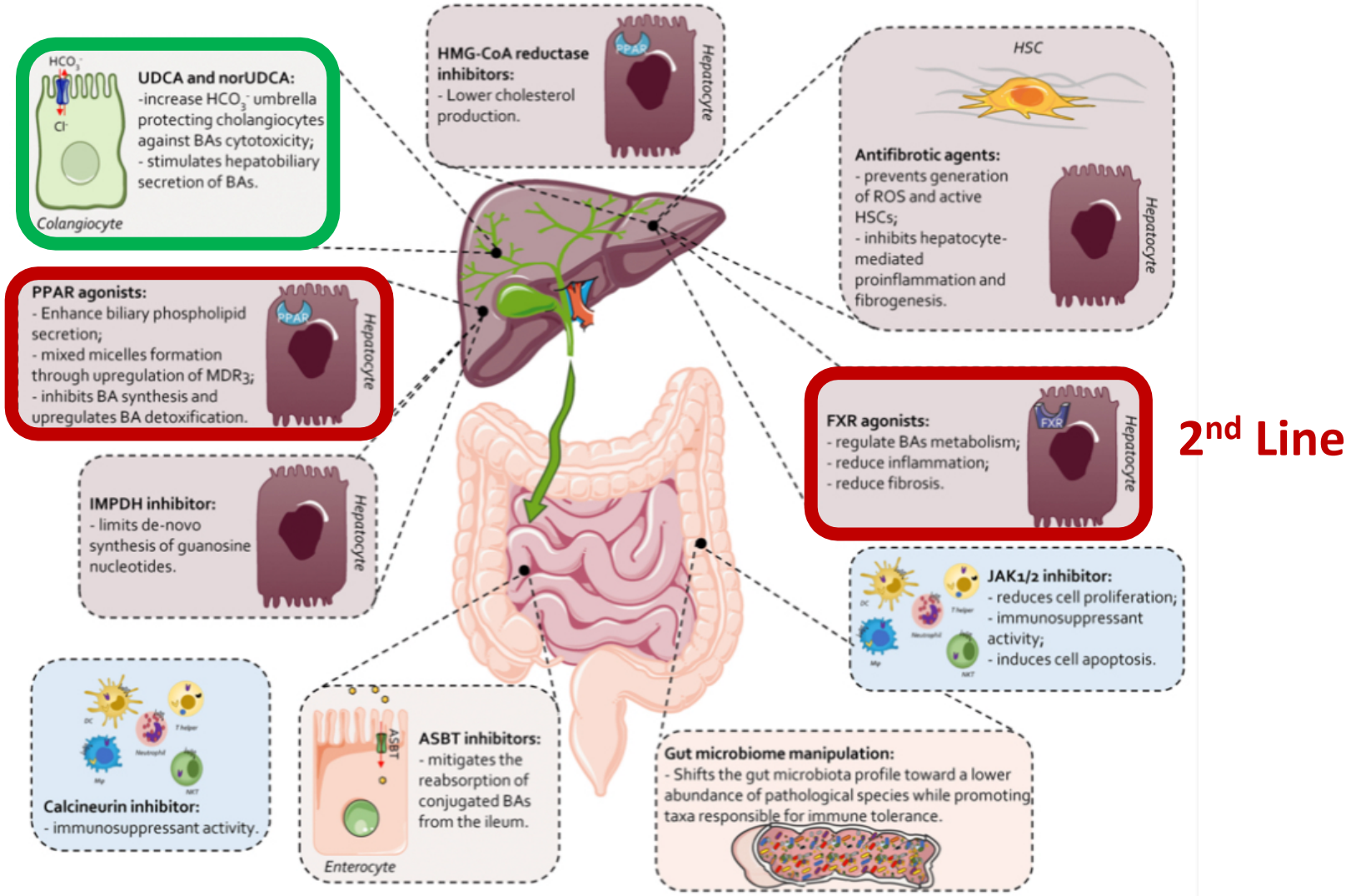
Question

- **What would you do next?**

Treatment

1st Line

2nd Line



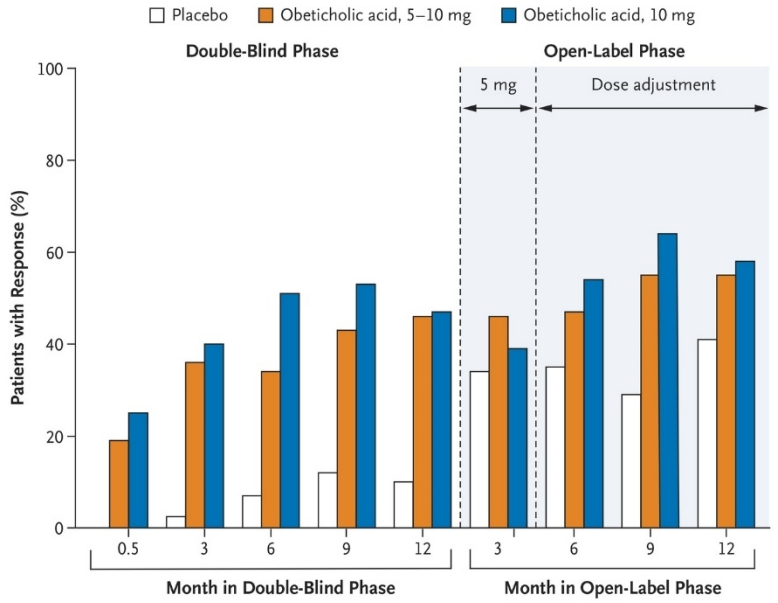
2nd Line

Fiorucci S, et al. Cells 2024; 13(18):1580.

Obeticholic acid (OCA)

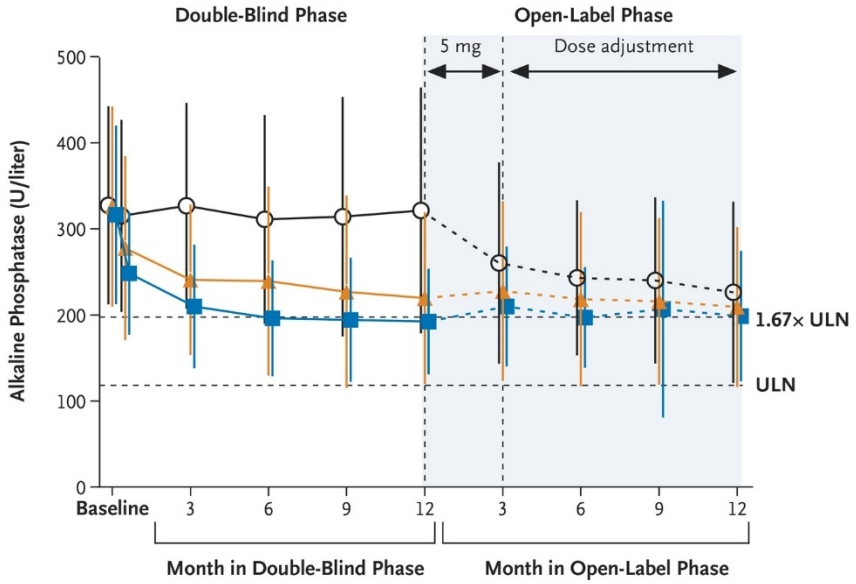
- 316 PBC (93% on UDCA)
  - 20% cirrhosis
  1) Placebo (n=73)
  2) OCA 5mg -> 10mg (n=71)
  3) OCA 10 mg (n=73)
- Open-label after 12 mo

Adverse Events	Placebo	OCA 5mg	OCA 10mg
Any SAE	3 (4%)	11 (16%)	8 (11%)
Pruritus	28 (38%)	39 (56%)	50 (68%)



No. of Patients

Placebo	73	73	73	73	73	64	60	59	59
Obeticholic acid, 5–10 mg	70	70	70	70	70	63	62	62	60
Obeticholic acid, 10 mg	73	73	73	73	73	64	59	61	59



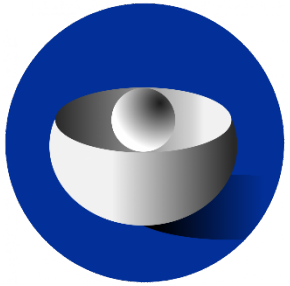
Nevens F, et al. N Engl J Med 2016; 375:631-643.

OCA Safety Concerns

2016 FDA approves OCA as second line therapy for PBC

2018 Black Box Warning
Give OCA 5-10mg once or twice weekly in patients with CP B / C cirrhosis or previous decompensation event

2021 Contraindication (FDA strongest warning)
OCA should NOT be used in PBC patients with advanced cirrhosis, defined as current or prior evidence of decompensation (HE, coagulopathy) or portal hypertension (ascites, varices, persistent thrombocytopenia)



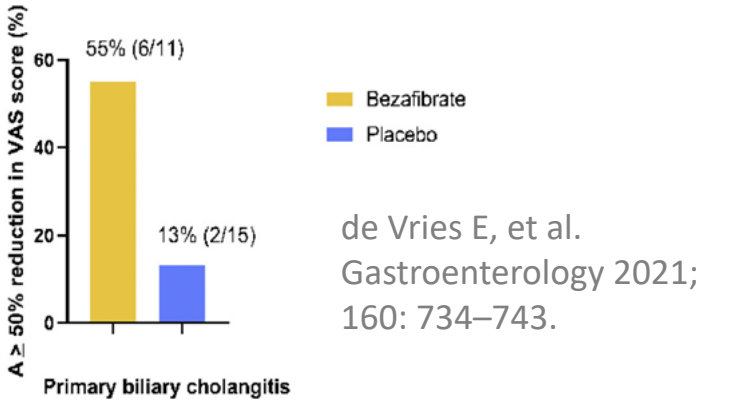
2024 European Medicines Association recommends that marketing authorization for OCA be revoked, because its benefits are no longer considered to outweigh its risks

Bezafibrate

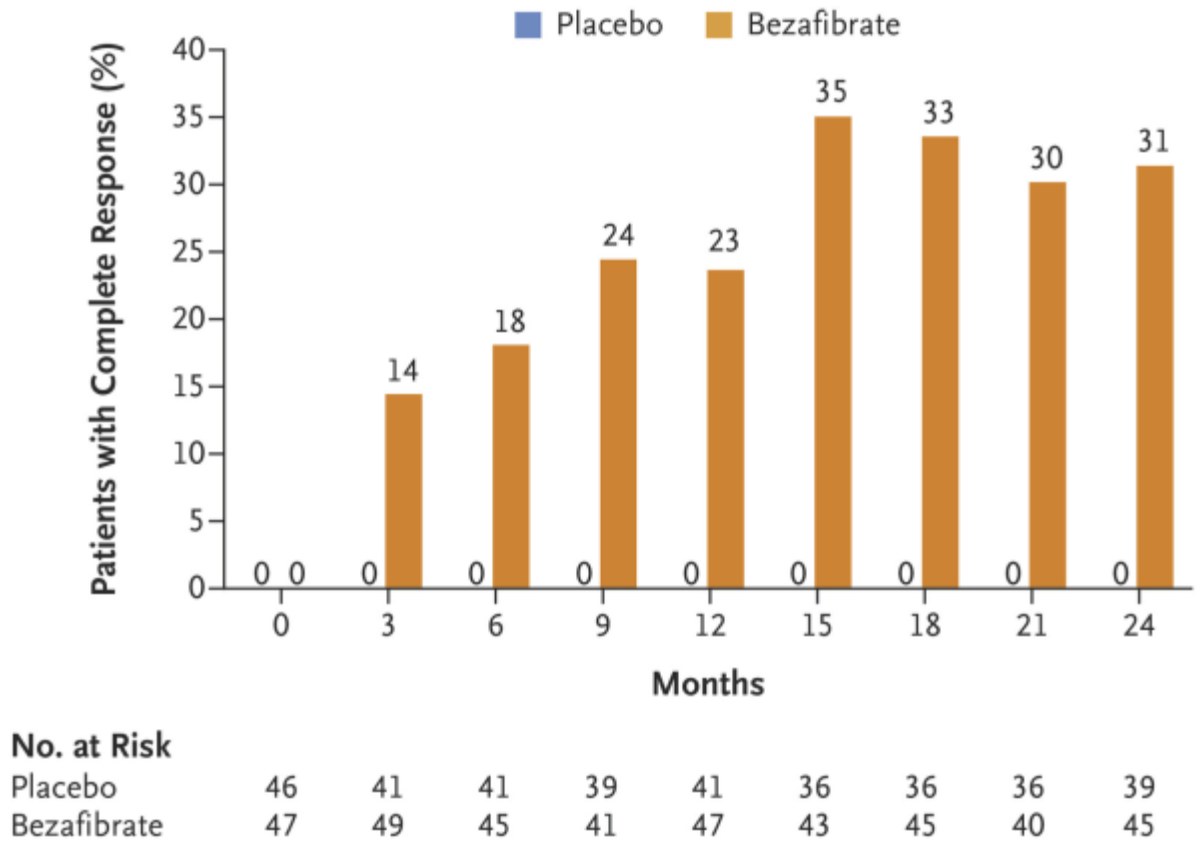
- 100 PBC on UDCA x 6 mo
  - ALP > 1.5 ULN or bili > ULN
  - 20% cirrhosis
    1) Placebo (n=50)
    2) Bezafibrate 400mg (n=50)

Adverse Events	Placebo	Bezafibrate
Any SAE	12 (24%)	14 (28%)
ALT >5x ULN	1 (2%)	3 (6%)
CK >5x ULN	0	1 (2%)
Creatinine worse	0	1 (2%)

FITCH study
DB-RCT bezafibrate or placebo x 21 days



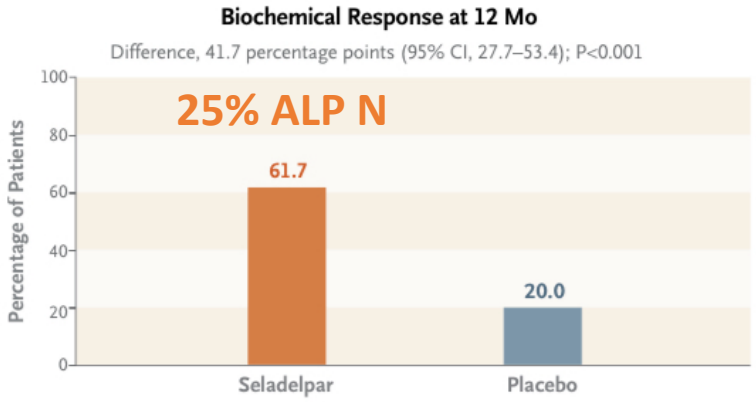
de Vries E, et al. Gastroenterology 2021; 160: 734–743.

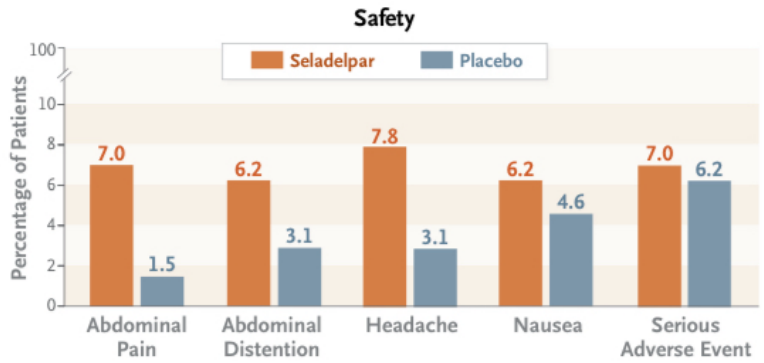


Corpechot C, et al. N Engl J Med 2018; 378: 2171-2181.

Seladelpar

128 vs 65 (14% cirrhosis)

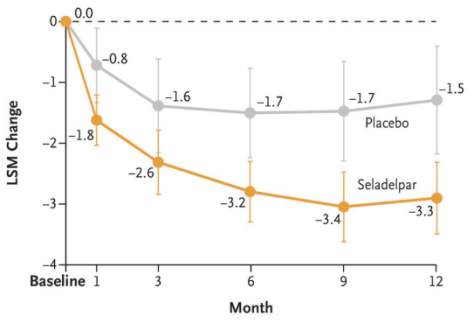


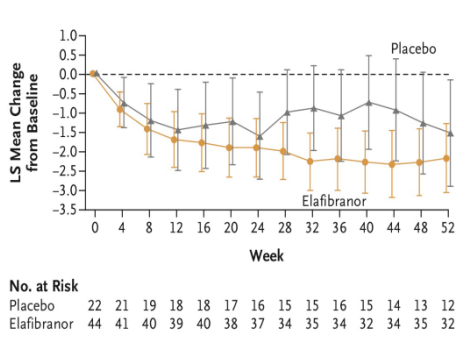


ALT, CK, Creatinine

Pruritus

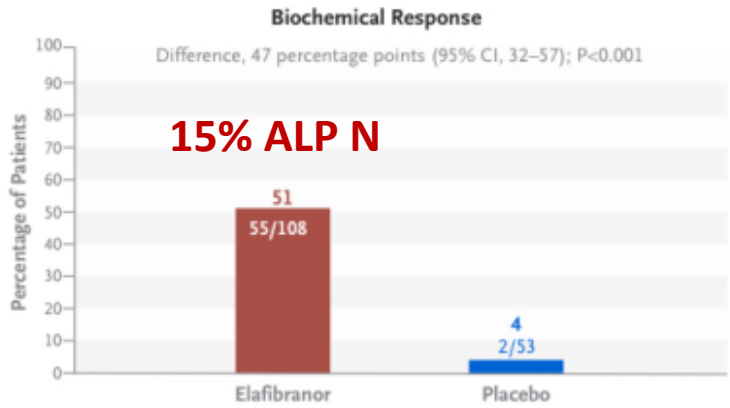
≥4 / 10





Elafibranor

108 vs 65 (35% cirrhosis)



4 stop due to CK
1 rhabdomyolysis

Hirschfield GM, et al. N Engl J Med 2024; 390(9): 783-794.

Kowdley KV, et al. N Engl J Med 2024; 390(9): 795-805.

CHAPTERS

I. Autoimmune Hepatitis

II. Primary Biliary Cholangitis

III. Immune-mediated Injury from Checkpoint Inhibitors

2 years later

- AZA, UDCA and seladelpar
  - AIH and PBC in clinical and biochemical remission
  - Creatinine and CK normal
  - Pruritus is better
  - Cirrhosis remains well compensated
- Dermatology appointment discover atypical nevus
- Biopsy = invasive melanoma
- Staging CT scan confirms metastasis to liver and lungs

Questions

1) Is it safe for Amber to receive immunotherapy?

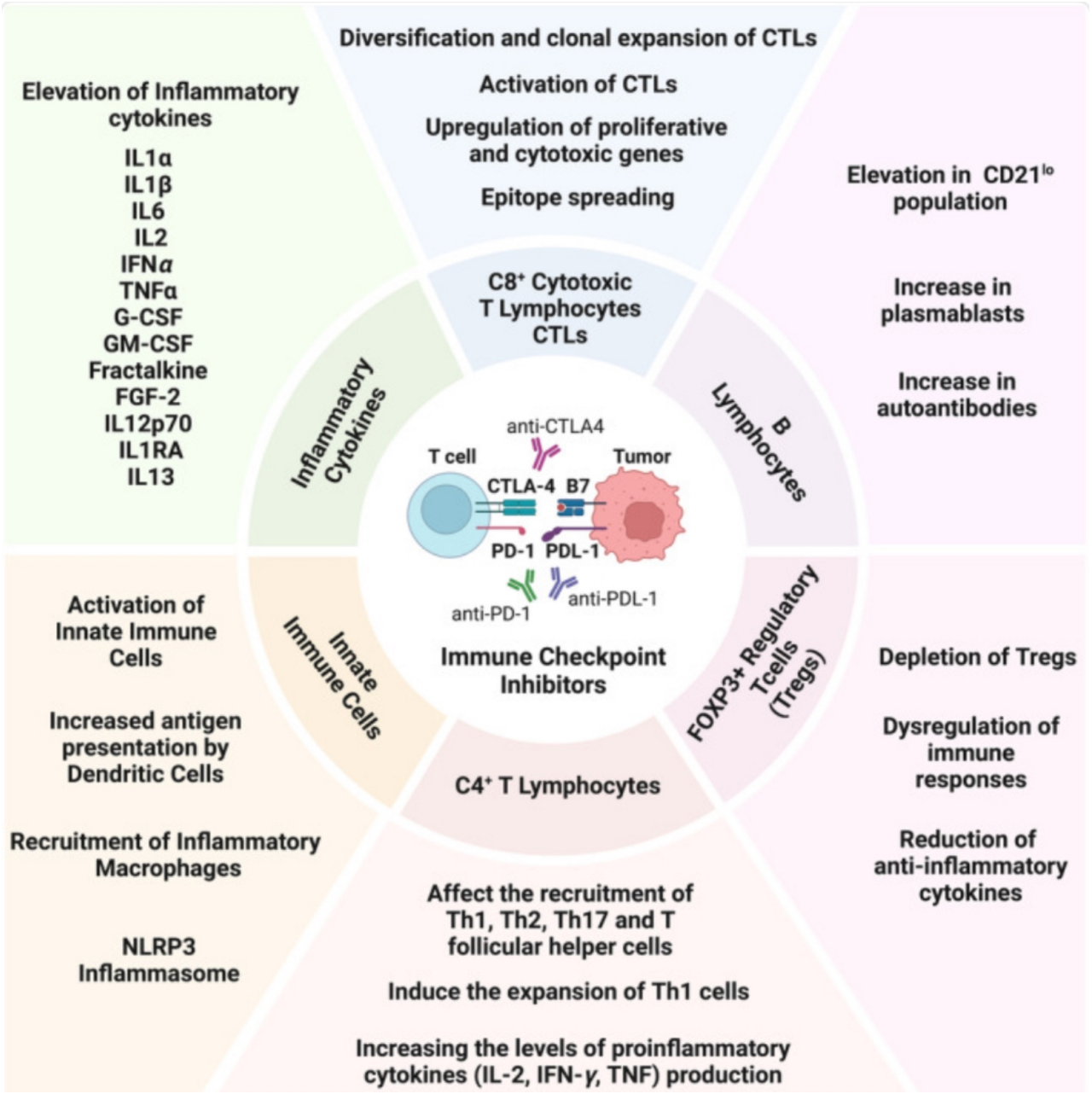
2) Should she be placed on steroids as prophylaxis?

3) How would you manage ILICI if it developed?

ICIs

- Abnormal liver tests <5%
- Estimated 50% of cancer patients will be exposed

- Mechanisms complex
  - Cytotoxic T cell activation attack of liver cells
  - Adaptive and innate immunity involved



Dara L, De Martin E. Liver Intl 2025; 45: e16198.

Risk Factors

- Two ICIs
- Female sex (OR 1.49, 95%CI 1.24-1.78, p=0.001)[1]
- Younger age
- Melanoma
- Pre-existing liver disease (MASLD, HBV)
- Pre-existing autoimmune liver disease
  - 8/22 (36%) patients with AI liver disease developed ILICI (none Grade 3-4)[2]

- **Risk factors should not preclude the use of these drugs**
  - **identify patients who should have closer monitoring**

[1]Unger JM, et al. J Clin Oncol 2022; 40(13): 1474-86.
[2]Kocheise L, et al. Front Immunol 2023; 14: 1326078.

Dara L, De Martin E. Liver Intl 2025; 45: e16198.

Presentation

1) Hepatocellular injury
   - Most common – mild, moderate, severe
   - Steroids
2) Cholestatic injury – more common with anti-PD1 (e.g. pembrolizumab)
   - Can resemble sclerosing cholangitis (MRCP)
   - UDCA – recommended by ESMO but not ASCO guidelines
3) Mixed

- **Important to exclude other causes including alcohol, drugs, viral, biliary obstruction (US) and monitor liver tests closely**

Dara L, De Martin E. Liver Intl 2025; 45: e16198.

Management

Hospital Admission

Consider Biopsy

Grade 1	Grade 2	Grade 3	Grade 4
ALT < 3 x ULN Bili < 1.5 x ULN	ALT 3 – 5 x ULN Bili 1.5 – 3 x ULN	ALT 5 – 20 x ULN Bili 3 – 10 x ULN	ALT > 20 x ULN Bili > 10 x ULN Ascites or HE
• Continue ICI if asymptomatic	• Hold ICI • 0.5-1 mg/kg oral prednisone	• Hold ICI • 1-2 mg/kg IV methylprednisolone	• Permanently stop ICI • 1-2 mg/kg IV methylprednisolone
• Symptoms or labs improving • Close monitoring	• Taper steroids over 4-6 weeks • Resume ICI	• Taper steroids over 4-6 weeks • ??? Resume ICI	• Refractory after D3 add MMF, AZA, TAC • ATG if fulminant

Adapted from Dougan M et al, Gastroenterology 2021; 160:1384-1393 and Dara L, De Martin E. Liver Intl 2025; 45: e16198.

Effect of corticosteroid dosing on outcomes in high-grade immune checkpoint inhibitor hepatitis

Retrospective cohort study, patients with grade ≥3 immune checkpoint inhibitor hepatitis (n=215)

Median dose: **2 mg/kg/day** methylprednisolone equivalents

n=87

n=128

Median dose: **1 mg/kg/day** methylprednisolone equivalents

NO difference in development of steroid-refractory hepatitis
OR 1.2, 95% CI 0.8-1.9, p=0.37

NO difference in time to resolution of hepatitis
HR 1.1, 95% CI 0.8-1.5, p=0.61

Higher-dose group MORE likely to develop steroid-related complications
- Hyperglycemia requiring treatment: RR 3.0, 95% CI 1.5-6.0, p<0.01
- Infection: RR 2.6, 95% CI 1.2-5.6, p=0.01

Li M, et al. Hepatology 2022; 75(3): 531-540.

Follow Up

1) **Is it safe for Amber to receive immunotherapy?**
   - **Maybe** – at least 1/3 chance of flare or ILICI

2) **Should she be placed on steroids as prophylaxis?**
   - **Unknown** – some would consider steroids

3) **How would you manage ILICI if it developed?**
   - **Depends** – on the severity

Take home messages

- **Liver biopsy**
  - needed for diagnosis of AIH and is helpful before withdrawal of immunosuppression
  - helpful in some cases of PBC and ILICI

- **AIH** = prednisone + AZA → MMF
- **PBC** = UDCA → PPAR agonists

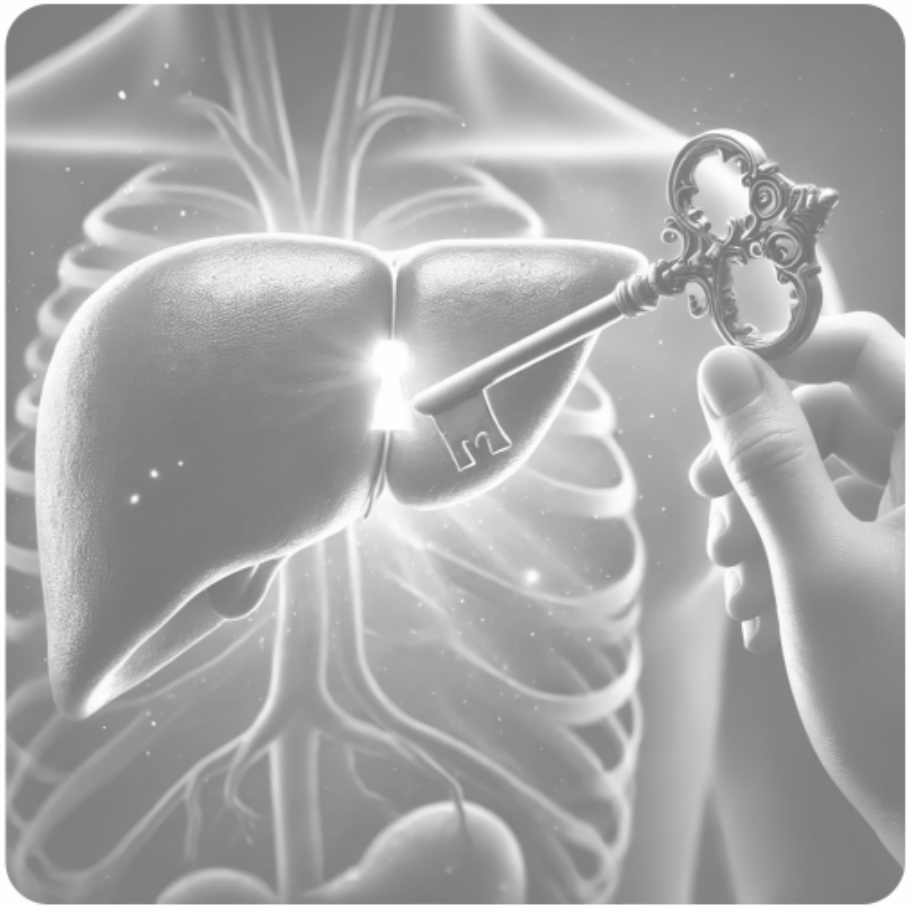
- **Severe ILICI** = IV methylprednisolone (max 1mg/kg)

CHAPTERS

I. Autoimmune Hepatitis

II. Primary Biliary Cholangitis

III. Immune-mediated Injury from Checkpoint Inhibitors



The End