AASLD THE LIVER MEETING®
2018 SAN FRANCISCO
NOVEMBER 9-13

Progress in Autoimmune Liver Diseases and Their Management

David A. Sass, MD FAASLD
Professor of Medicine
Sidney Kimmel Medical College
Medical Director, Liver Transplantation
Thomas Jefferson University Hospitals

Jefferson
Philadelphia University + Thomas Jefferson University

Disclosures

- I have no conflicts of interest

Agenda

Autoimmune Offerings at AASLD 2018

- Primary Biliary Cholangitis (PBC)
  - General Hepatology Update
    ("New Paradigms for an Old Disease"; Cynthia Levy, MD)
  - 3 Oral presentations
  - 32 Poster presentations
- Primary Sclerosing Cholangitis (PSC)
  - 2 Oral presentations
  - 18 Poster presentations
- Autoimmune Hepatitis (AIH)
  - 1 Oral presentation
  - 23 Poster presentations
  - SIG programming topic ("Advancing AIH Understanding and Care"; Chris Bowlus, MD Chair)

1. Primary Biliary Cholangitis

HEPATOLOGY

AASLD

PRACTICE GUIDANCE | HEPATOLOGY, VOL. 0, NO. 0, 2018

Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases

Keith D. Lindor,[1] Christopher L. Bowlus,[2] James Boyer,[3] Cynthia Levy,[4] and Marlyn Mayo[5]

Clinical Practice Guidelines

CrossMark

EASL | JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis☆

European Association for the Study of the Liver*

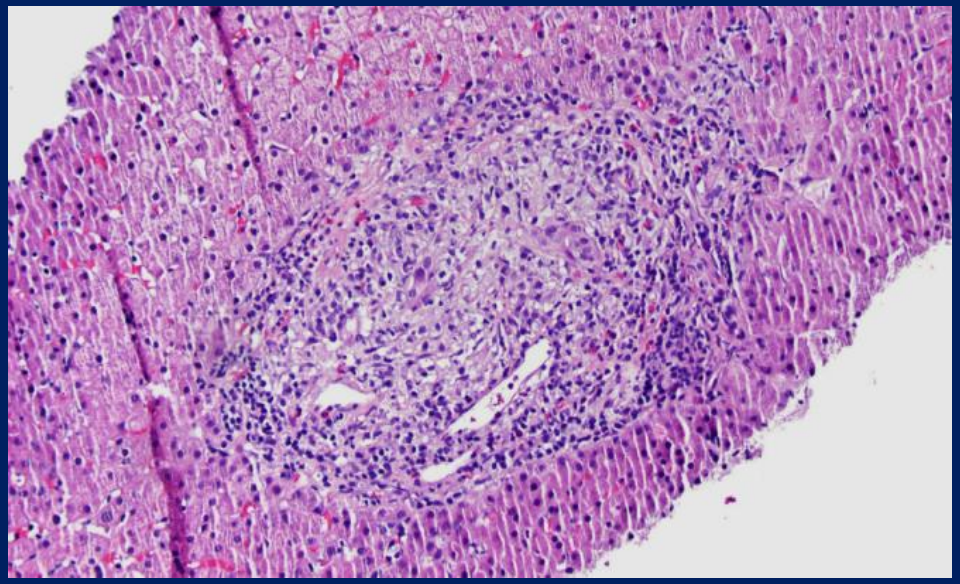
Journal of Hepatology **2017** vol. 67 | 145–172

Primary Biliary Cholangitis (PBC)

- Chronic cholestatic liver disease
- Autoimmune in nature
- Inflammation and destruction of small interlobular bile ducts
- Affects predominantly middle-aged females
- Rising incidence and prevalence
- Most common symptoms: pruritus, fatigue and sicca symptoms
- Name change in 2015

PBC Diagnosis
(need 2 out of these 3 criteria)

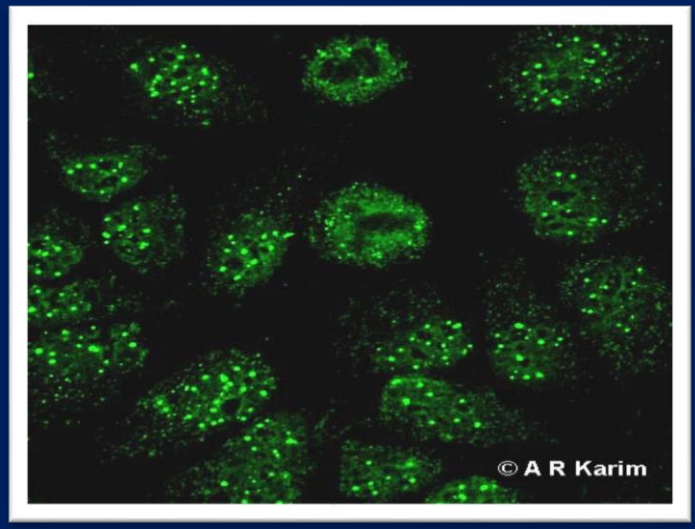
- Unexplained elevation of ALP > 1.5 x ULN
- Positive AMA
- Non-suppurative destructive cholangitis on histology



ANA with PBC Specificty
(present in 20% cases)

- Nuclear Rim
  Main Ag is gp-210

- Multiple nuclear dots
  Main Ag is Sp-100



GLOBE score

GLOBALPBC.COM
THE GLOBAL PBC STUDY GROUP

Calculate GLOBE score

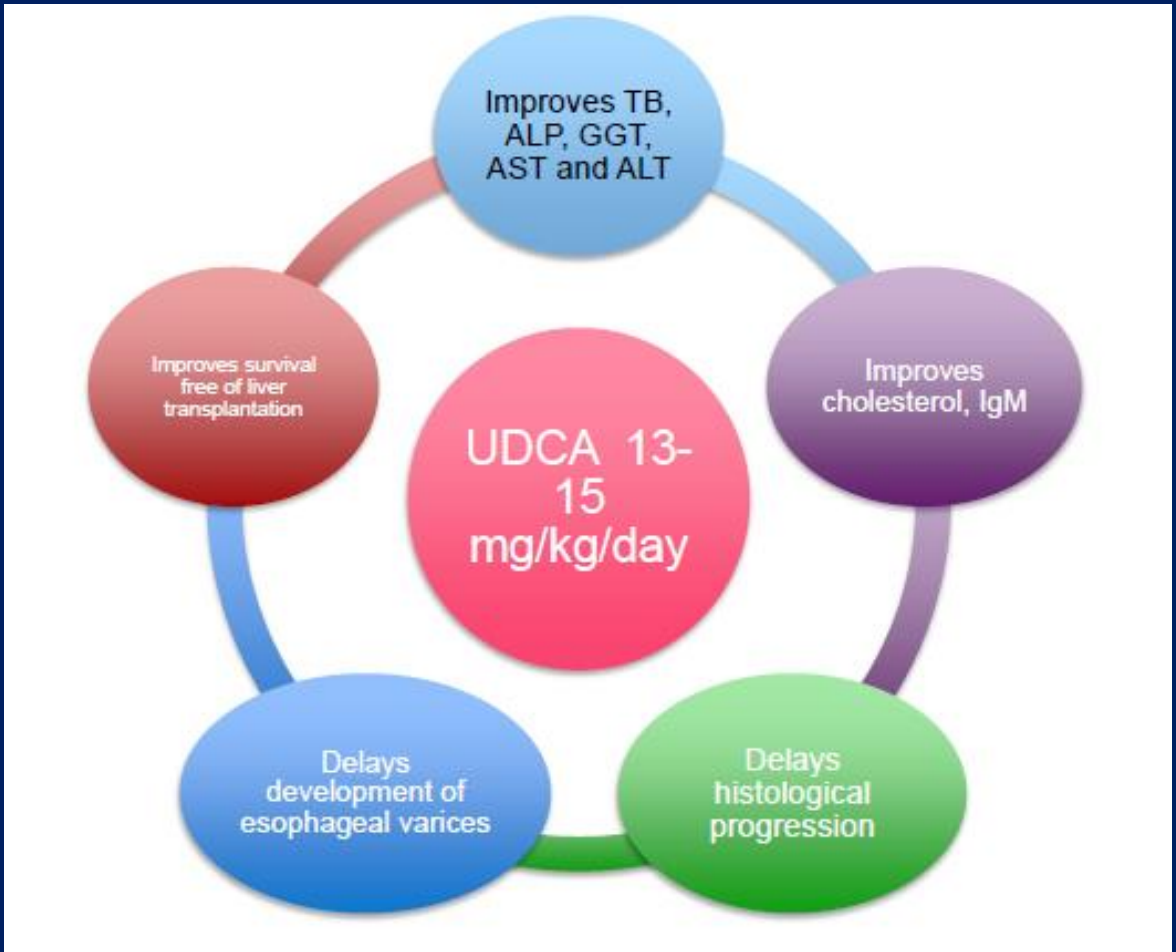
Home | Philosophy | Who we are | The disease | Publications | GLOBE | Funding | Contact

The GLOBE score for patients with Primary Biliary Cholangitis (PBC)

The GLOBE score is an internationally relevant and validated risk assessment tool, able to stratify PBC patients to high and low risk.

Age, years *at initiation of UDCA therapy*			
Total bilirubin level, µmol/L or mg/dl *after one year of UDCA therapy*		Upper limit of normal:	
Alkaline phosphatase level, U/L *after one year of UDCA therapy*		Upper limit of normal:	
Albumin, g/L *after one year of UDCA therapy*		Lower limit of normal:	
Platelets, x 10^9/L *after one year of UDCA therapy*			

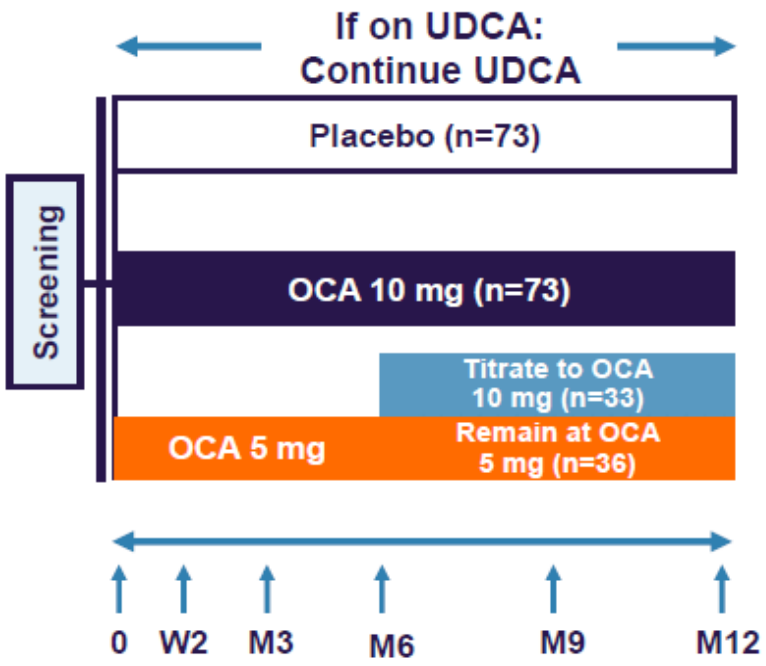
1st Line: UDCA



Start UDCA 13-15 mg/kg/day
- monitor liver chemistries
- ~ 40% inadequate response

From: Levy C and Lindor KD, in *Zakim and Boyer's Hepatology: A Textbook of Liver Disease, Elsevier 2011;738-53*

2nd Line: Obeticholic Acid (OCA)
Poise Trial



Randomization Strata

Subjects stratified 1:1:1 by:

1) ALP >3x ULN and/or AST >2x ULN and/or total bilirubin >ULN (Paris I)
2) Not receiving UDCA treatment

- OCA Titration at 6 Months: Subjects in OCA titration arm titrated from 5 mg to 10 mg at Month 6 if they met any of the following criteria at the Month 6 assessment:
  1. The primary endpoint (ALP <1.67x ULN or bilirubin ≤ULN) was not achieved
  2. No evidence of tolerability issues, e.g. pruritus

Nevens F. et. al. NEJM 2016;375:7

OCA Dosing Recommendations

OCA Dose	Disease Stage	
	Non-cirrhotic or compensated cirrhosis (Child-Pugh A)	Decompensated cirrhosis, Child B or C (including prior decompensation)
Starting dose – 1st 3 months	5 mg/day	5 mg/week
Dose titration at 3 months	10 mg/day	5 mg twice a week, at least 3 days apart May increase to 10 mg twice a week, at least 3 days apart

PBC: Management Flow Chart

EASL
European Association for the Study of the Liver

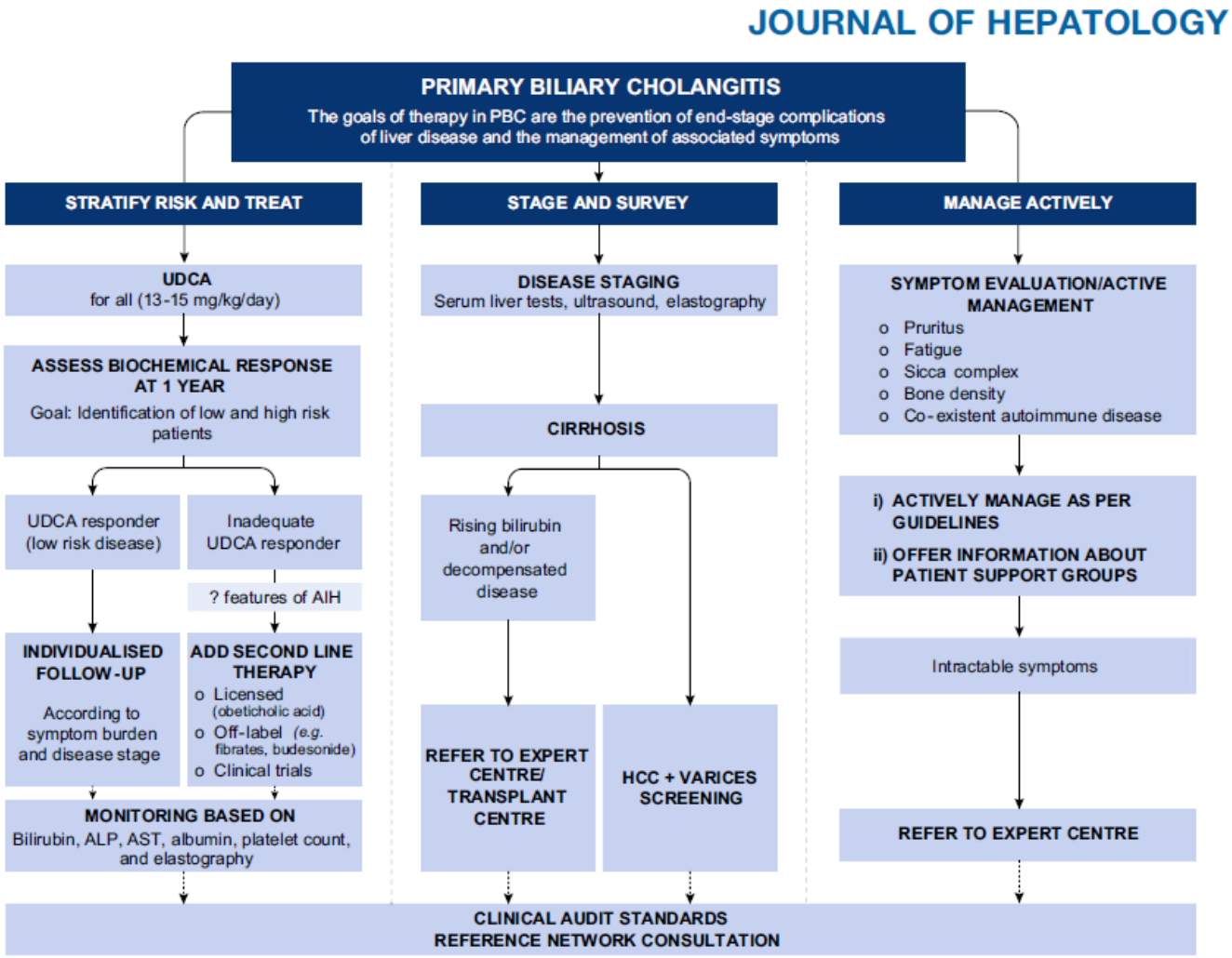


Fig. 4. EASL Clinical practice guideline in PBC consensus management flow chart. In patients with PBC, a structured approach to their life-long care is i recommended. Care should focus around three 'pillars' of practice, a) stratification of risk and treatment; b) staging and surveying disease; and c) a management. Whilst care always needs to be tailored to the individual patient and the health care environment, these three guiding themes are central to eff

Journal of Hepatology 2017 vol. 67 | 145–172

PPAR Agonists (Fibrates & Seladelpar)

Drug	PPAR isoforms affected	Mechanism	Summary of Findings
Fenofibrate	α	• Downregulation HNF4➔ decreased CYP7A1 activity • Downregulation NF-KB➔ decrease in TNF- α • Upregulation MDR3➔ Increased secretion of phospholipids	• Decreases markers of cholestasis • Decreases IgM • Lowers TNF- α levels • Lowers TG
Bezafibrate	Pan-PPAR	• As above + • PXR agonist➔ further downregulation of CYP7A1 • PPAR γ activation modulates lipid metabolism➔ insulin sensitization	• Decreases markers of cholestasis and inflammation • Improvement of pruritus • Improvement in liver stiffness
Seladelpar	δ	• Improves insulin sensitivity➔decreased lipid accumulation in the liver • Induces weight loss • Reduces markers of inflammation • Reduces stellate cell activation	• Improves markers of cholestasis • Improves markers of inflammation • Improves LDL-C
Elafibranor	α and δ	• Improves insulin sensitivity➔ decreased lipid accumulation in the liver • Induces weight loss • Reduces markers of inflammation • Reduces stellate cell activation	• To be determined

Efficacy and safety of seladelpar in PBC: 52-week analysis from a randomized phase 2 study

- **Objective**
  Safety and Efficacy of Seladelpar
- **Methods**
  Randomized, OL, dose-ranging, Phase 2 study for 52 weeks of Seladelpar in pts with PBC in patients with IR or intolerance to UDCA (with ALP > 1.67x ULN)
- **Conclusions**
  Potent anti-cholestatic effect - generally safe, well-tolerated and not associated with pruritus

  Median ALT ↓: -31% and -33% in the 5/10 mg and 10 mg groups, respectively

1°and 2°outcomes

Seladelpar	5/10 mg (n=17)	10 mg (n=17)
Baseline Mean/Med ALP	351/301 U/L	279/248 U/L
Responders* (n)	59% (10)	71% (12)
ALP Mean change	-47%	-46%
ALP Normalized (n)	24% (4)	29% (5)

* ALP < 1.67 x ULN, > 15% decrease ALP and TB < ULN

Bowlus C. et.al. (Abstract LB-3)

1923

A Real World Experience of Obeticholic Acid (OCA) Therapy in Patients with Primary Biliary Cholangitis (PBC) Treated in a Tertiary Care Liver Center

- Experience at one Tertiary MC (2016-18)
- N = 241 PBC patients followed
- OCA Rx in 35 patients
- 26.4% ALP reduction with stable Tbili after median 14 months
- 15% didn't fill Rx, 34% discontinued (mainly due to pruritus)
- 2 patients: progressive liver disease (? Drug-related)

- Detailed discussion with patient re OCA Rx
- Assistance on insurance approval
- Aggressive management of pruritus
- Close clinic follow-up

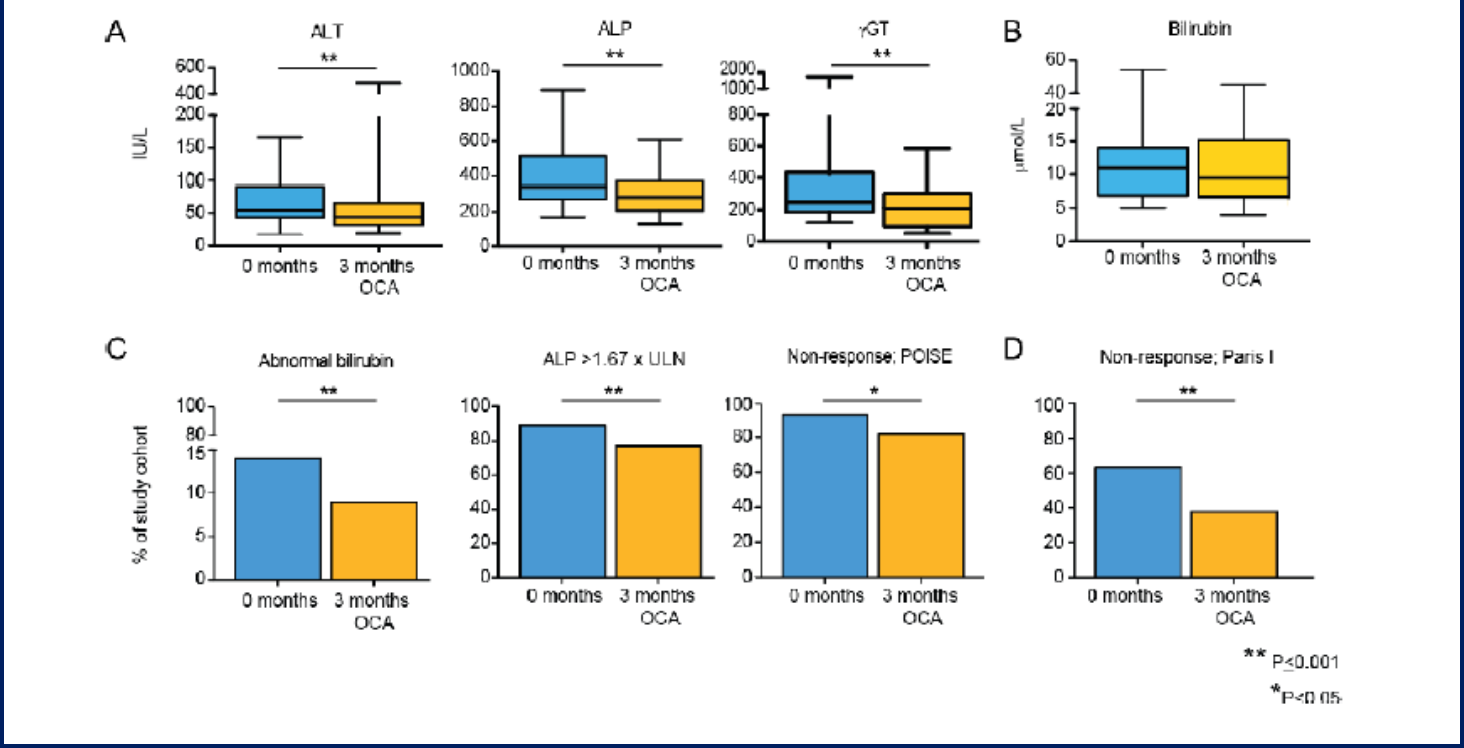
TO IMPROVE ADHERENCE AND ENSURE SAFETY

Yimam, KK et. al. California Pacific Medical Center

1925

The UK-PBC Audit of Real-World Obeticholic Acid Use in Patients with Primary Biliary Cholangitis (PBC)

- To assemble early, real-world data on implementation of OCA use across UK
- 9 units assessed (5/17-5/18)… 3 month interim analysis
- 82 patients commenced OCA Rx (56 completed 3 months of treatment)



Trivedi P. et.al. for UK-PBC Group

1931

Hepatic Safety Overview of Obeticholic Acid for the Treatment of Patients with Primary Biliary Cholangitis

- POISE data studied to determine if evidence that OCA contributes to hepatotoxicity in PBC patients +/- cirrhosis

Table: POISE Hepatic Disorders Adverse Events† (DB Phase and OLE)

Adverse Events	DB Placebo n= 73 n* (%)	DB Titration OCA n= 70 n* (%)	DB 10 mg OCA n= 73 n* (%)	OLE Total OCA‡ (n=193) n* (%)
Ascites	0	1 (1%)	1 (1%)	8 (4%)
Esophageal varices hemorrhage	0	0	0	3 (2%)
Portal hypertensive gastropathy	0	0	0	4 (2%)
Varices esophageal	1 (1%)	1 (1%)	0	10 (5%)
Hepatic cirrhosis	0	0	0	3 (2%)
Hepatomegaly	0	0	0	3 (2%)
Portal hypertension	0	0	0	3 (2%)
Blood alkaline phosphatase increased	0	0	0	4 (2%)
Hepatic enzyme increased	0	0	0	3 (2%)

†AEs ≥2%; Percentages are based on the total number of patients during the OLE.
‡Safety Population (data cutoff 27 Dec 2017).
* Patients reporting more than one AE within a special interest category, system organ class, or preferred term are counted only once per dose group.
Note: Hepatic Disorders are events included in the Hepatic Disorders Standardized MedDRA query (SMQ), excluding the following sub-SMQs: Congenital, familial, neonatal and genetic disorders of the liver; Hepatitis, non-infectious; Liver infections; and Pregnancy-related hepatic disorders.

CONCLUSIONS:

- More patients experienced AE's during the 36 months OLE

- Annualized rate of decompensations were low

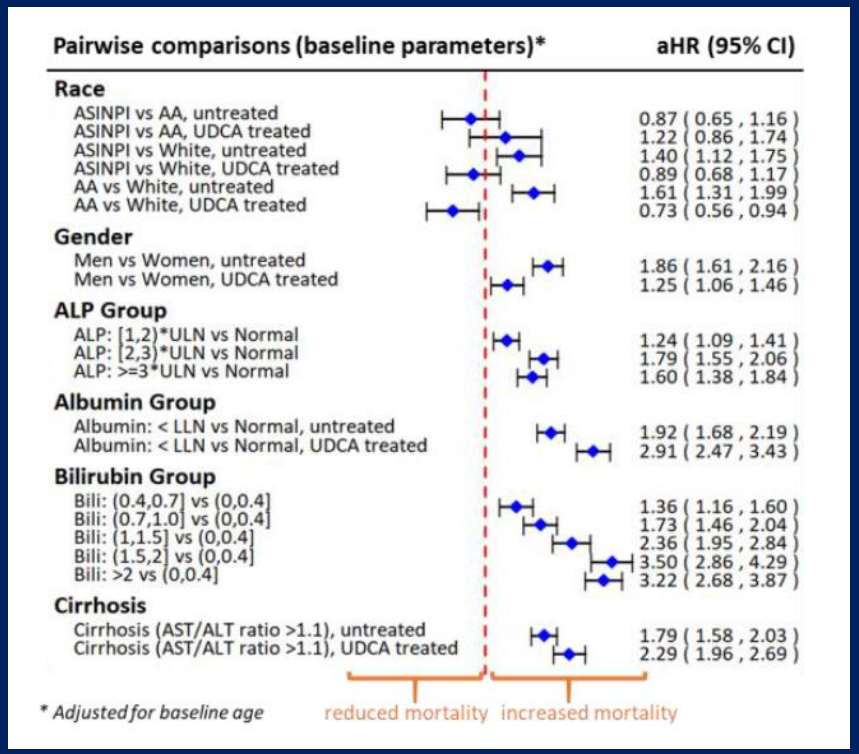
- eDISH analysis showed no evidence of hepatic injury with OCA

Pockros PJ et.al. for POISE Group

47

Serum Bilirubin within Normal Range Is Associated with an Increasing Risk of Mortality in Patients with Primary Biliary Cholangitis Regardless of Ursodeoxycholic Acid Treatment

- Aim: Impact of BRN, race, gender and UDCA use on risk of all-cause mortality in PBC in 11 US health systems (n=4243)
- Methods: IPTW to adjust for UDCA selection bias, Cox-regression analysis
- Results: BRN level strongly and positively associated with ↑ mortality (BRN > 0.7)
  - after IPTW UDCA Rx associated with ↓ mortality
- Conclusions: regardless of UDCA Rx, high-normal BRN (0.7-1.0) is associated with 2x risk of death c/w BRN < 0.4

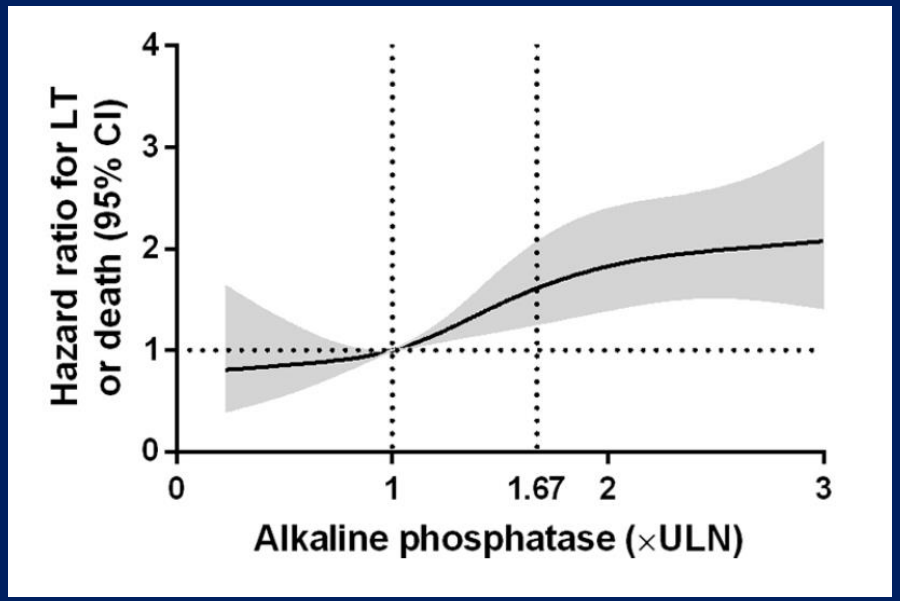


Gordon SC et.al. for the Fibrotic Liver Disease Consortium

1909

Alkaline Phosphatase Normalization Is Associated with a Decreased Risk for Liver Transplantation and Death in Patients with Primary Biliary Cholangitis

- ALP < 1.67 regarded as acceptable "surrogate endpoint that is reasonably likely to predict clinical benefit"
- Aim: to evaluate whether ALP levels < 1.67 x ULN are associated with further improvement in TFS: utilized data from Global PBC Study Group cohort (17 centers Europe and NA)



Perez CFM et.al. for Global PBC Study Group

CONCLUSIONS

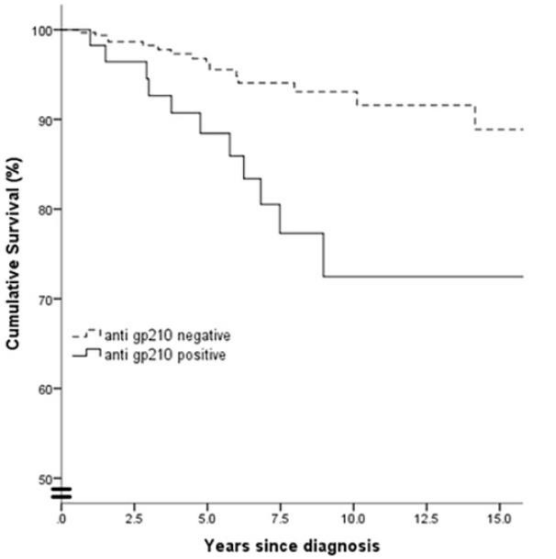
- Reaffirms that ALP has a log-linear association as a surrogate marker of outcome in PBC

- Targeting ALP normalization in future trials: predicted to be associated with added clinical benefit

1926

Antibodies to gp210 and Understanding Risk in Patients with Primary Biliary Cholangitis.

- Analysis of immunoprofiles of 499 PBC patients at a tertiary care center (2001-17); 86% AMA (+)
- 4.2% had PBC-specific ANA's (gp210 and sp100)



Numbers at risk

	Years since diagnosis				
	0.0	2.5	5.0	7.5	10.0
anti gp210 negative	317	255	153	108	64
anti gp210 positive	61	52	39	24	13

Only anti-gp210 predicted an adverse presenting phenotype

Their presence: predictive of all-cause death (HR 2.89, p=0.011)

Thus: meaningful risk marker in PBC patients

Haldar D et.al. for Birmingham, UK Group

2. Primary Sclerosing Cholangitis

CME

ACG Clinical Guideline: Primary Sclerosing Cholangitis

Keith D. Lindor, MD, FACG[1,2], Kris V. Kowdley, MD, FACG[3] and M. Edwyn Harrison, MD[2]

VOLUME 110 | MAY 2015 www.amjgastro.com

Seminar

CrossMark

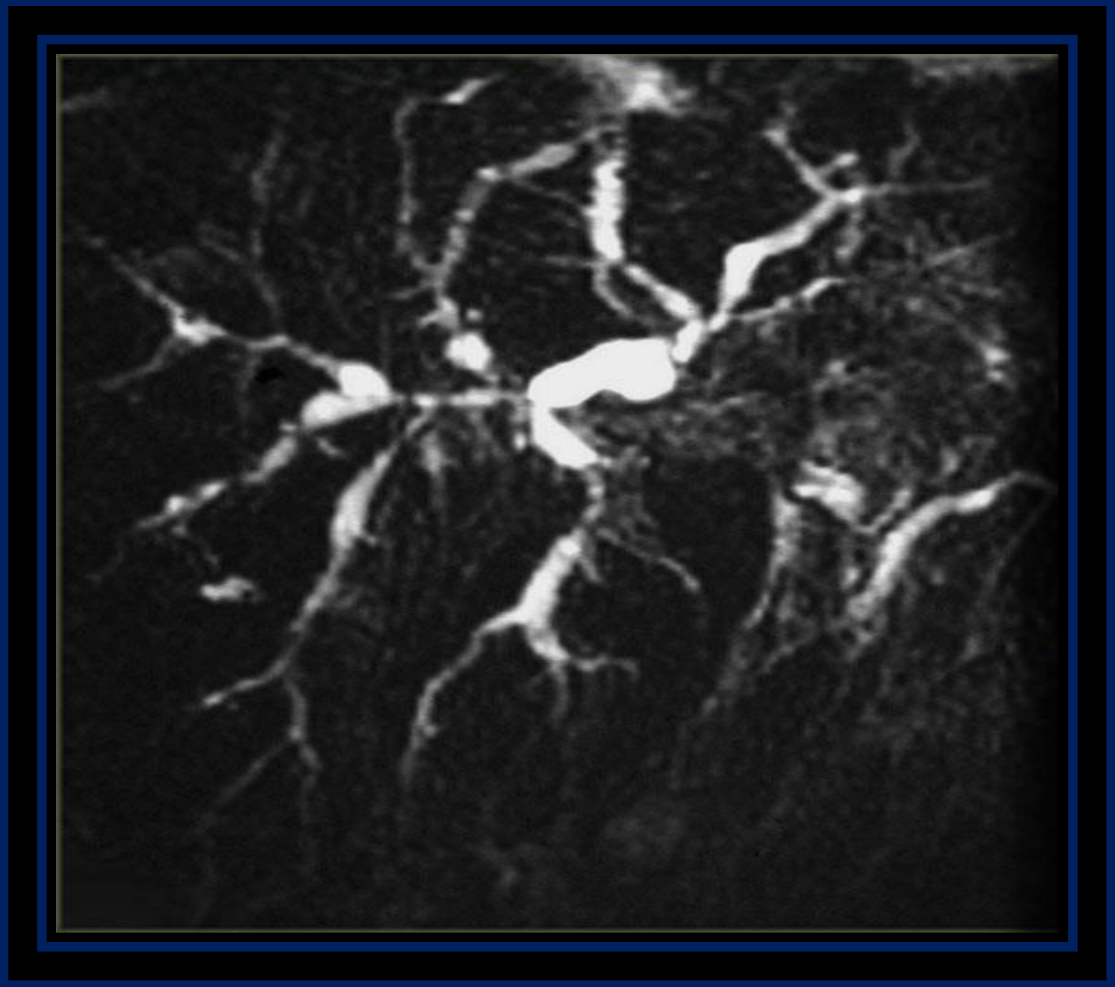
EASL | JOURNAL OF HEPATOLOGY

Primary sclerosing cholangitis – a comprehensive review

Tom H. Karlsen[1,2,3,*], Trine Folseraas[1,3], Douglas Thorburn[4,5], Mette Vesterhus[1,6]

Journal of Hepatology **2017** vol. 67 | 1298–1323

Primary Sclerosing Cholangitis (PSC)



- Cholestatic liver disorder of biliary structuring
- Male predominance
- Variable clinical presentation & rate of progression
- Usually diagnosed by MRCP/ERCP (liver biopsy seldom needed)

- 60-85% PSC → IBD
- 2.5-5% IBD → PSC

PSC: Differential Diagnosis

- Cholangiocarcinoma
- IgG4-related cholangitis
- HIV cholangipoathy
- Ischemic cholangitis
- Portal hypertensive biliopathy
- Secondary sclerosing cholangitis

PSC: Treatment

- No approved or proven medical therapy!

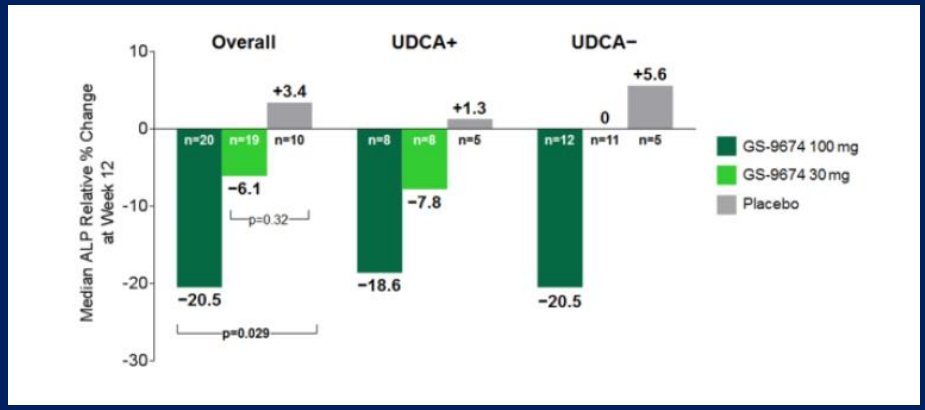
- Endoscopic management:
  - ERCP w balloon dilation for dominant strictures and/or cholangitis
  - Dominant stricture on imaging: ERCP with cytology, biopsies and FISH
  - Antibiotic prophylaxis peri-procedurally

43

The Non-Steroidal Farnesoid X Receptor (FXR) Agonist GS-9674 Improves Liver Biochemistry and Decreases Serum Bile Acids in Patients with Primary Sclerosing Cholangitis (PSC): A Phase 2, Randomized, Placebo-Controlled Trial

- Objective: safety and efficacy of GS-9674 in patients with PSC (Phase 2)

- Methods:
  - DBRPCT comparing 2 doses of GS-9674 and PBO x 12 weeks
  - 52 non-cirrhotics with large-duct PSC and ALP > 1.67 x ULN



- Main Findings:
  GS-9674: ↓ ALP irrespective of UDCA use
  GS-9674 ↓ ALT, GGT, TIMP-1, C4 and BA's
  Grade 2-3 pruritus less frequent with GS-9674 c/w PBO

CONCLUSIONS:
GS-9674 led to significant ↓ in liver biochemistry and markers of cholestasis without aggravating pruritus in PSC patient

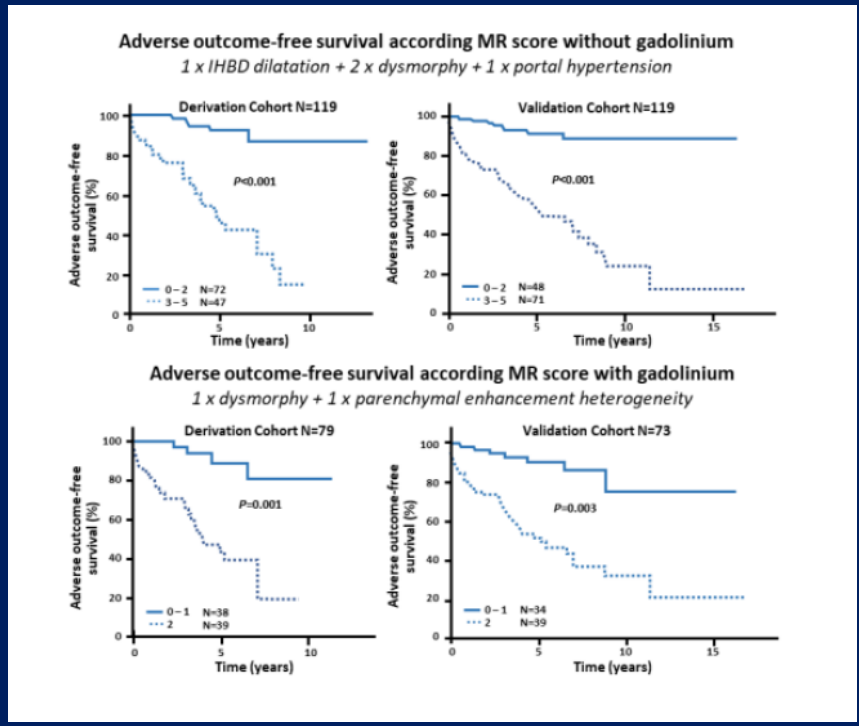
Trauner M et. al.

44

AASLD Foundation Abstract Award recipient

Two Simple Magnetic Resonance Scores Are Able to Predict Survival in Patients with Primary Sclerosing Cholangitis

- Aim: To assess the clinical prognostic value of 2 MR risk scores (built to predict radiologic progression in PSC)
- Methods: Central reviewing of first available MR imaging of 2 cohorts of PSC patients, calculation of 2 scores, determination of prognostic value of scores by using composite endpoint (LRD, OLT, Cirrhosis Decompensation)
- Conclusions: Two MR risk scores are able to predict adverse outcome-free survival in PSC… could be applicable in future clinical trials



Cazzagon N. et. al.

3. Autoimmune Hepatitis

Clinical Practice Guidelines

EASL | JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Autoimmune hepatitis☆

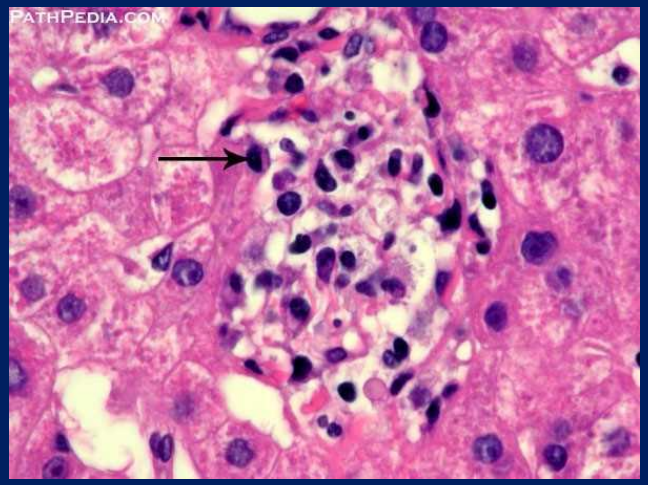
European Association for the Study of the Liver*

Journal of Hepatology **2015** vol. 63 | 971–1004

Autoimmune Hepatitis (AIH)

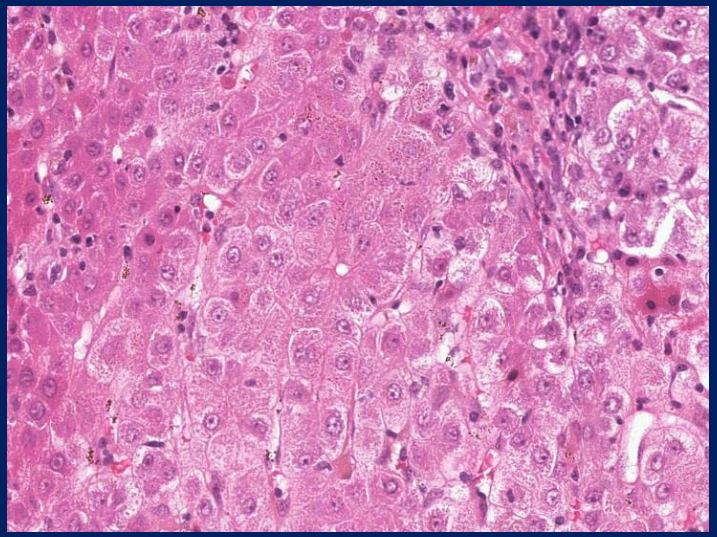
- Unresolving inflammation of the liver of unknown cause
- Female predominant disease
- Clinical spectrum is wide: ranges from asymptomatic presentation to acute, severe liver failure
- Diagnosis: clinical, laboratory (abnormal globulins/ autoantibodies) and histologic features
- Treatment: prednisone +/- azathioprine

AIH: Histologic Hallmarks

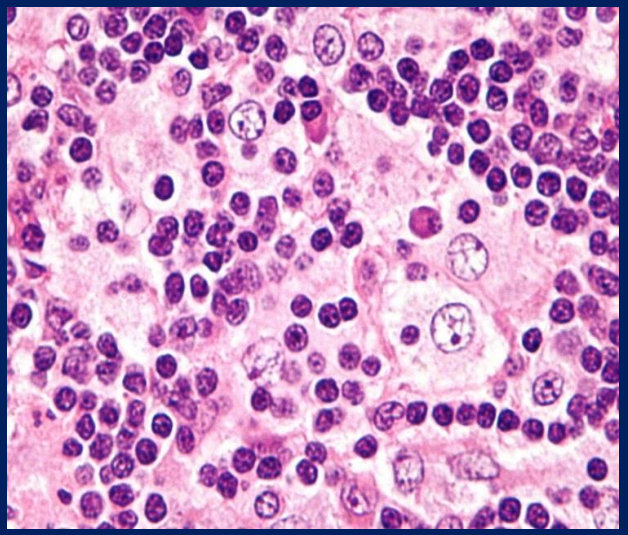


None are pathognomonic

Interface hepatitis with dense plasma cell infiltrate

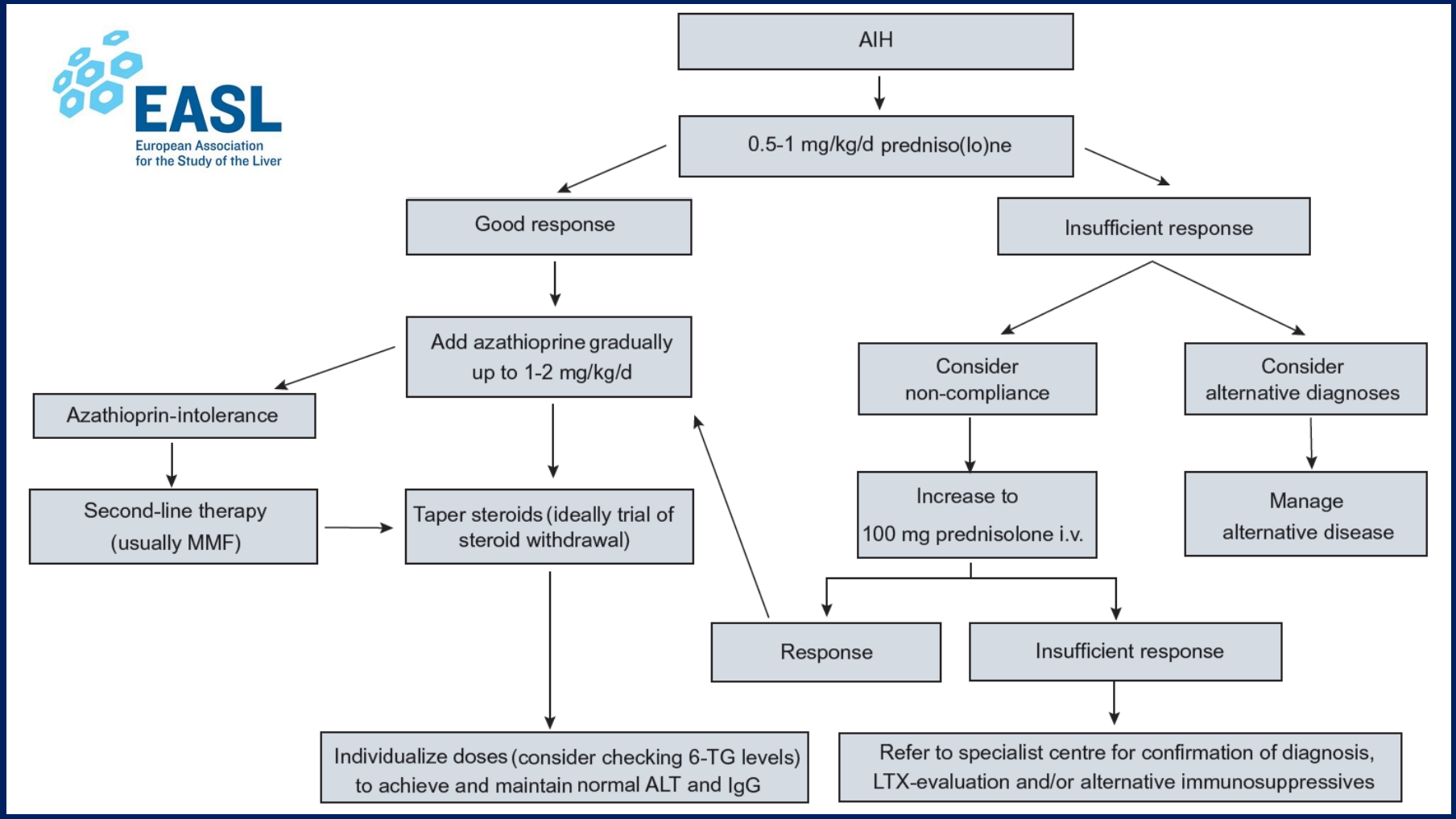


Hepatocellular Rosette formation



Emperipolesis

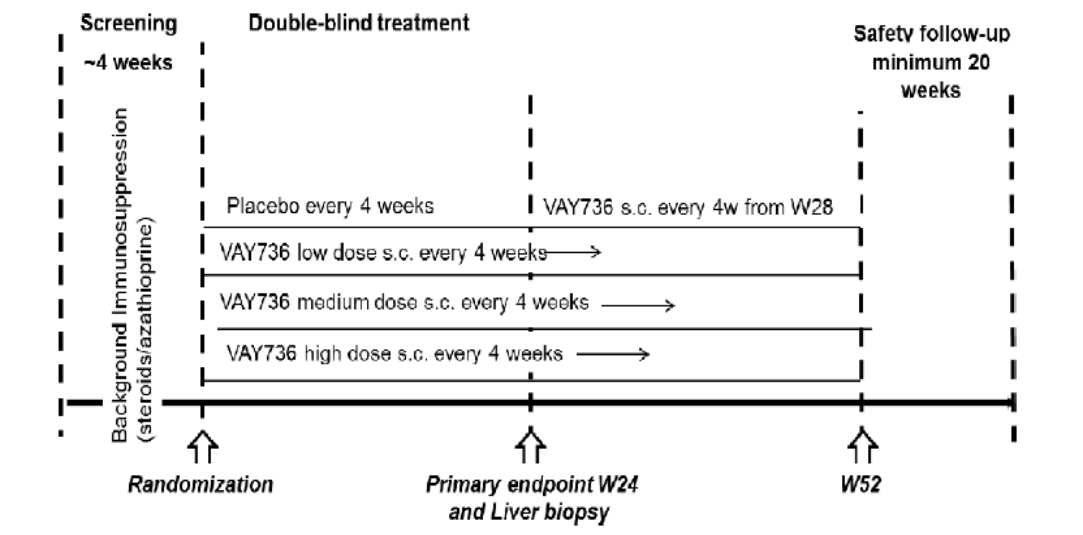
Therapeutic Strategy in AIH (Combination of steroids and AZA)



1967

AMBER- a Novel Phase 2/3 Trial of Ianalumab, a Human Anti-BAFF Receptor Antibody, in Autoimmune Hepatitis, NCT03217422

- Aim/background: New and better tolerated Rx's needed to control disease activity in AIH patients
  - Several lines of evidence support B-cell targeting in AIH
- Ianalumab (VAY736) is a human monoclonal Ab against BAFF receptor (dual activity: B cell depletion and BAFF receptor blockade)
- Methods: Part 1: Phase 2 RPCDBDR study in patients with IR to standard therapy (20 pts in each of 3 arms)
- Concl: Part 2 (will be a Phase 3 study with selected dose)



Jones DE et.al.

1973

Clinical Characteristics of Antinuclear Antibody-Positive Hepatocellular Type Drug-Induced Liver Injury and Autoimmune Hepatitis

- Background: DILI: an important cause of ALF
  - New molecular targeted drugs/ immune checkpoint inhibitors have caused new types of DILI
  - Study to compare ANA (+) DILI vs AIH
- Methods:
  - 17 patients with ANA (+) DILI and 167 patients with AIH (Dx: 1977-2017)
  - compared demographics, biochemical, serological and pathological data
- Results:
  IgG titer significantly higher in AIH group (p=0.004)
  ALT significantly higher in ANA (+) DILI group (p=0.014)
  ANA (+) DILI: “acute hepatitis” inflammation lobule-predominant (rather than portal). Plasma cell portal infiltrate and Rosetting: less in ANA (+) DILI group
- Conclusion: IgG level, ALT and liver histology may be useful in distinguishing the 2 entities

Sasaki C. et.al.

“Overlap” or “Variant” syndromes

- Low prevalence
- Lack of universal agreement on definition

Impractical to perform randomized controlled trials in this setting

1975

The Clinical Characteristics and Long-Term Outcomes for Patients Having Autoimmune Hepatitis Overlap Syndromes

- Background/Aim: little data on clinical characteristics, long-term outcomes, survival and need for OLT in patients with various AI overlap syndromes

- Methods: single center, patients followed from 1988-2017

- Results/Conclusion:
  - no survival difference ; 3-year LT-free survival 58%, 82% and 64% respectively (p=0.45)
  - AIH/PBC who presented with AIH first had lower TFS than PBC first or AIH/PBC simultaneously (p=0.001)
  - Liver decompensation: only predictor of mortality (p=0.02)

Table 1: Demographics and clinical characteristics between different AIH overlap syndromes

	AIH/PBC (n=86)	AIH/PSC (n=22)	AIH/SDPSC (n=11)	p-value
Female	75 (87.2%)	13 (59.1%)	5 (45.5%)	<0.001
AMA positive	57 (66.3%)	2 (9.1%)	0 (0%)	<0.001
ANA positive	52 (60.5%)	10 (45.5%)	6 (54.5%)	0.97
ASMA positive	46 (53.5%)	13 (59.1%)	2 (18.2%)	0.12
Immunosuppression	65 (75.6%)	18 (81.8%)	8 (72.7%)	0.45
Ursodeoxycholic	76 (88.4%)	15 (68.2%)	5 (45.5%)	0.001
Treatment response	49 (57.0%)	8 (36.4%)	6 (54.5%)	0.11
Cirrhosis at diagnosis	29 (33.7%)	6 (27.3%)	7 (63.6%)	0.14
Decompensation	19 (22.1%)	6 (27.3%)	3 (27.3%)	0.74
Liver transplant	5 (5.8%)	6 (27.3%)	2 (18.2%)	0.01
Age at diagnosis	55.2±12.4	38.2±17.1	44.5±14.0	<0.001
ALT at diagnosis	148.7±151.1	289.1±419.5	286.7±383.0	0.03
AST at diagnosis	151.7±192.6	309.5±464.8	209.5±288.8	0.06
ALP at diagnosis	335.0±256.7	375.8±190.2	255.2±151.9	0.40
TB at diagnosis	2.5±3.2	3.7±4.5	3.7±4.5	0.27

Chayanupatkul et.al. Mount Sinai

Thank You