UPDATES IN CHOLESTATIC AND AUTOIMMUNE LIVER DISEASES AASLD 2016

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UPDATES

- Emerging therapies in cholestatic liver diseases
- Surrogate markers of disease progression in primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC)
- Management of refractory autoimmune hepatitis (AIH)

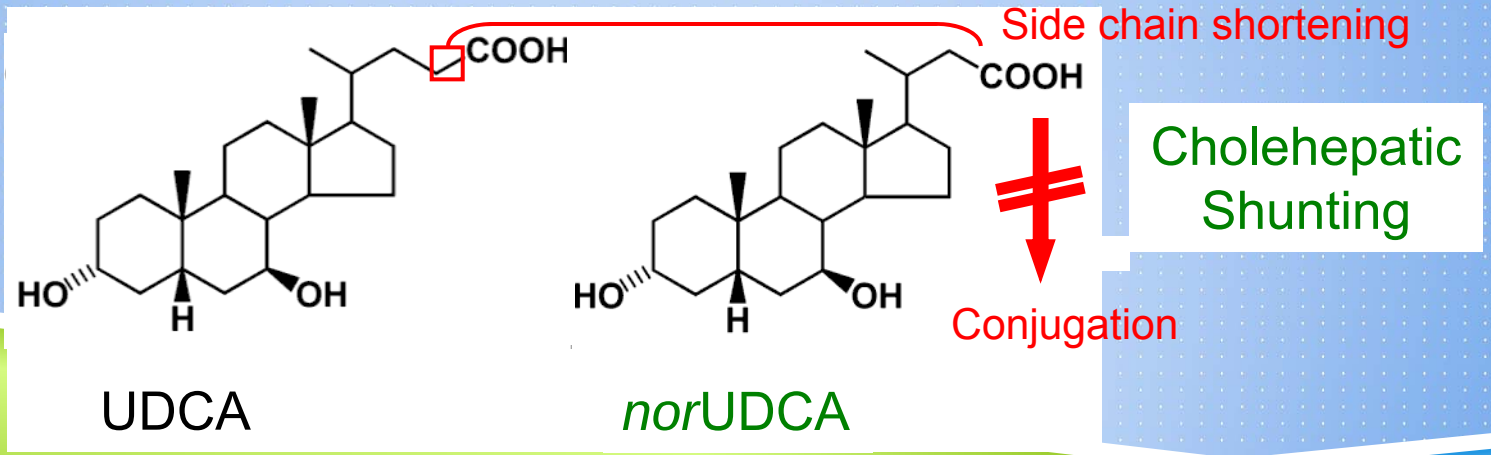
EMERGING THERAPIES
PSC

- Title: *nor*Ursodeoxycholic acid (norUDCA) improves cholestasis in PSC independent of ursodeoxycholic acid (UDCA) pre-treatment and response
- The European *nor*UDCA Study Group
- Phase II multicenter randomized control trial
  - 45 centers from 12 European countries

Trauner M, et al. AASLD 2016. Abstract 210.

BACKGROUND

- PSC is a chronic cholestatic disease of the liver and bile ducts; eventually leads to end-stage liver disease
- There is no approved medical therapy for PSC to date
- The role of UDCA in the treatment of PSC is still controversial
- 24-*nor*-UDCA is a side chain-shortened c23 homologue of UDCA

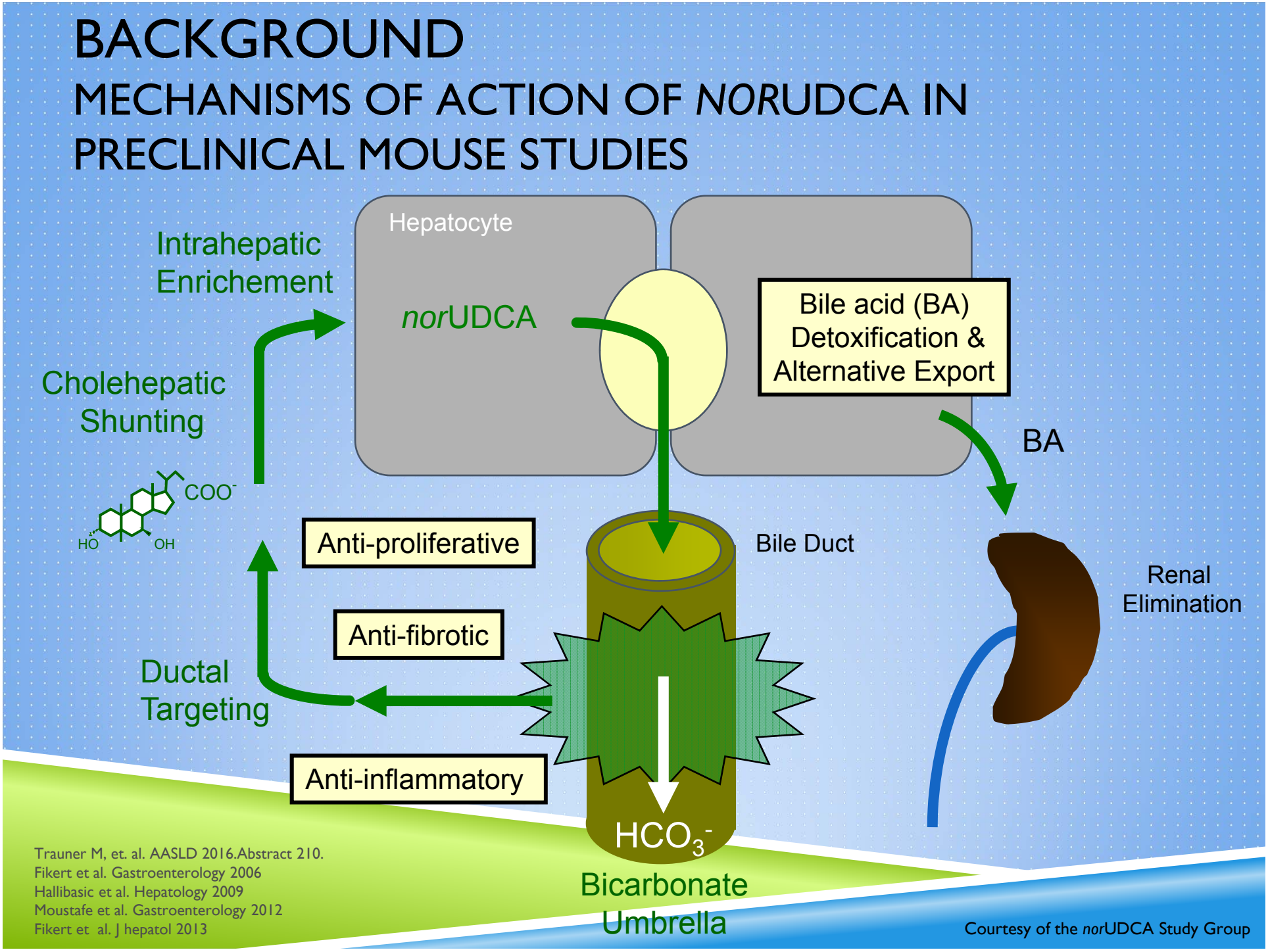


Yimam KK; Bowlus C. Autoimmunity reviews 13 (2014) 445-450.
Yoon et al. Gastroenterology 1986.
Hofmann et al. Hepatology 2005.

Courtesy of the *nor*UDCA Study Group

BACKGROUND

MECHANISMS OF ACTION OF *NOR*UDCA IN PRECLINICAL MOUSE STUDIES



Trauner M, et. al. AASLD 2016.Abstract 210.
Fikert et al. Gastroenterology 2006
Hallibasic et al. Hepatology 2009
Moustafe et al. Gastroenterology 2012
Fikert et al. J hepatol 2013

Courtesy of the *nor*UDCA Study Group

STUDY DESIGN

- Objectives
  - **Compare 500 mg/d, 1000 mg/d or 1500 mg/d of oral *nor*UDCA with placebo in the treatment of PSC**
  - Evaluate the safety and tolerability
  - Evaluate the impact of previous UDCA exposure and response on the therapeutic efficacy of *nor*UDCA
- Endpoints
  - Primary
    - **Mean relative change (%) in serum ALP between baseline visit and the end of treatment (EOT): week 12**
  - Secondary
    - Proportion of patients with partial normalization of ALP (≤ 1.5 ULN)
    - GGT, AST, ALT and serum bilirubin levels

Trauner M, et. al. AASLD 2016.Abstract 210.

STUDY DESIGN

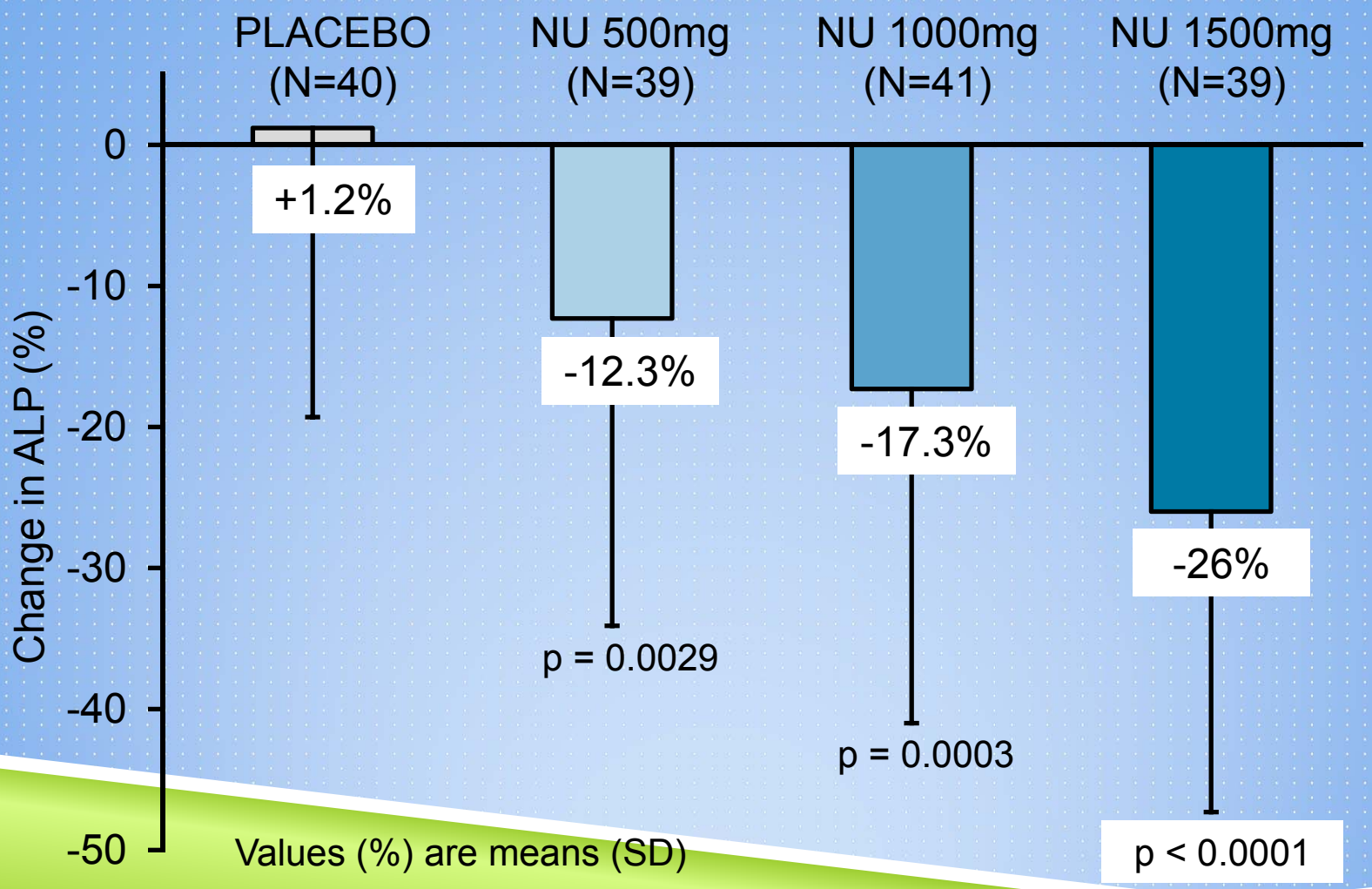
- Inclusion criteria
  - Male or female patients, age ≥ 18 and < 80
  - Cholestasis of at least 6 months of duration
  - **ALP ≥ 1.5 ULN at baseline**
  - Cholangiography or liver histology supporting diagnosis of PSC
  - PSC with or without IBD

- Exclusion criteria
  - Other causes of liver diseases/cholangitis; CCA
  - Use of immunosuppressant, biologics and fibrates
  - **Decompensated cirrhosis (Child B & C)**
  - Endoscopic treatment for dominant stricture

- **UDCA naïve or following 8 weeks of UDCA washout**

Trauner M, et. al. AASLD 2016.Abstract 210.

RESULTS (1): RELATIVE CHANGES IN ALP FROM BASELINE TO EOT (ITT: 159 PTS)

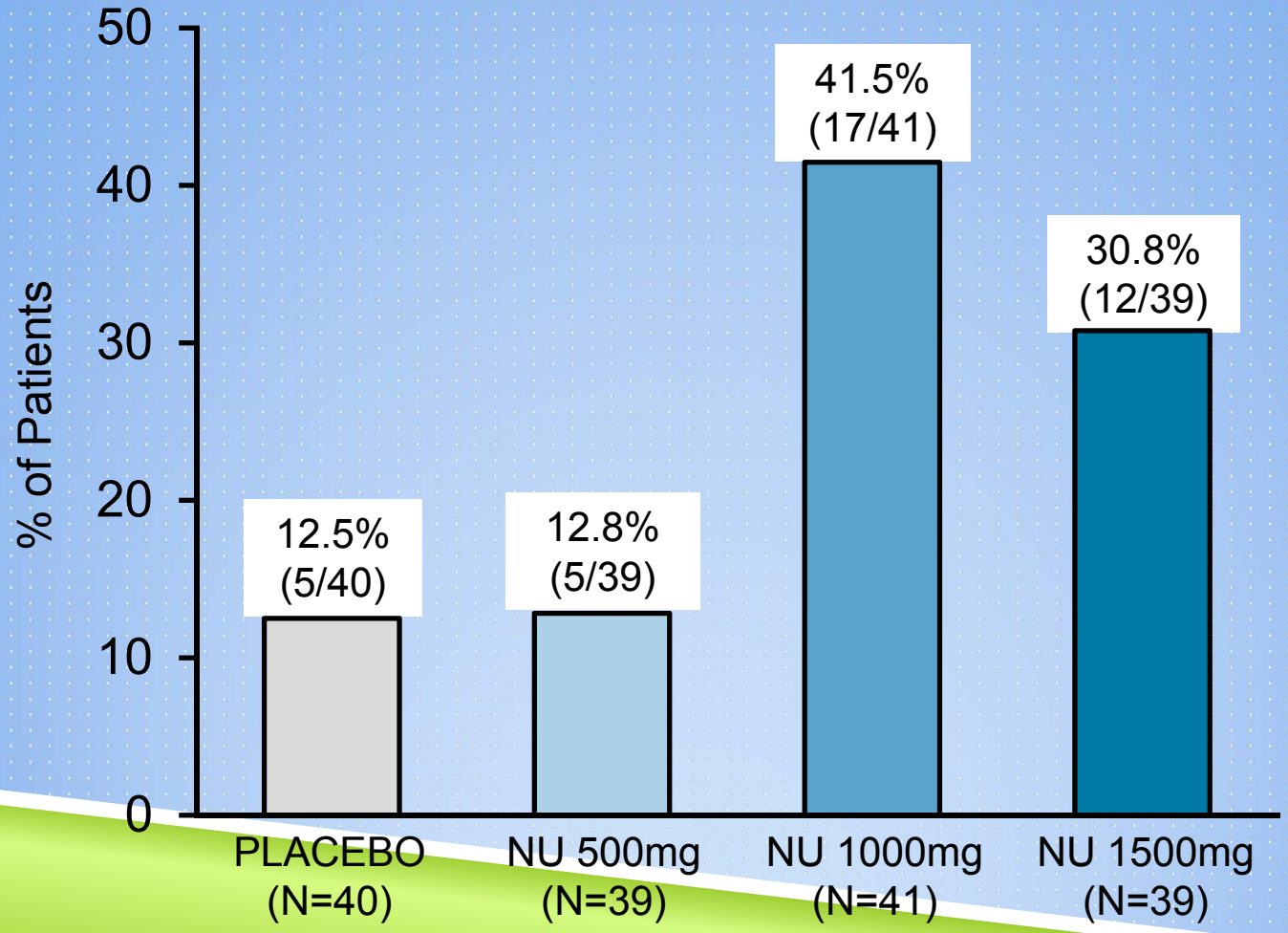


➢ ***nor*UDCA (NU) reduces ALP in a dose-dependent fashion**

Trauner M, et. al. AASLD 2016.Abstract 210.

Courtesy of the *nor*UDCA Study Group

RESULTS (2): PATIENTS (%) REACHING ALP ≤ 1.5 ULN (ITT)



Courtesy of the *nor*UDCA Study Group

Trauner M, et. al. AASLD 2016.Abstract 210.

*NOR*UDCA RESPONSE (Δ ALP % AT EOT) ANALYSIS: PREVIOUS UDCA EXPERIENCE

		PLACEBO (N=40)	NU 500mg (N=39)	NU 1000mg (N=41)	NU 1500mg (N=39)
UDCA Responder	Mean (N)	- 6.2% 18	- 9.9% 13	- 16.4% 14	- 19.5% 13
UDCA Non-responder	Mean (N)	- 3.5% 9	- 10.1% 15	- 14.9% 17	- 27.3% 14
UDCA Naive	Mean (N)	12.3% 12	- 14.9% 9	- 24.8% 9	- 32.0% 10

77% of previous UDCA responders and **79% of UDCA non-responders** had lowers-ALP levels under norUDCA at EOT compared to screening values when most patients were still on UDCA (69-75%)

Courtesy of the *nor*UDCA Study Group

Trauner M, et. al. AASLD 2016.Abstract 210.

RESULTS (3)

- Decrease in ALT, AST and GGT was observed in all treatment groups from baseline to ETO
- Response to NU was independent of gender, disease duration, baseline ALP and IBD

Trauner M, et. al. AASLD 2016.Abstract 210.

SAFETY
MOST COMMON ADVERSE EVENTS

TEAEs	PLACEBO (N=40)	NU 500mg (N=39)	NU 1000mg (N=41)	NU 1500mg (N=39)
Abdominal pain	5 (12.5%)	1 (2.6%)	4 (9.8%)	1 (2.6%)
Diarrhea	4 (10.0%)	0 (0.0%)	1 (2.4%)	3 (7.7%)
Fatigue	4 (10.0%)	2 (5.1%)	2 (4.9%)	5 (12.8%)
Nasopharyngitis	7 (17.5%)	6 (15.4%)	9 (22.0%)	8 (20.5%)
Arthralgia	4 (10.0%)	1 (2.6%)	1 (2.4%)	0 (0.0%)
Back pain	4 (10.0%)	1 (2.6%)	0 (0.0%)	3 (7.7%)
Headache	3 (7.5%)	2 (5.1%)	1 (2.4%)	7 (17.9%)
Pruritus	4 (10.0%)	3 (7.7%)	4 (9.8%)	6 (15.4%)

Number of Patients (%) with Treatment Emerging Adverse Events (TEAEs)

Trauner M, et. al. AASLD 2016.Abstract 210.

Courtesy of the *nor*UDCA Study Group

CONCLUSION

- *nor*UDCA resulted in a significant reduction of serum ALP values within 12 weeks of treatment compared to placebo
- The effect occurred in a dose-dependent manner with the highest effect at 1500 mg/d
- This effect was independent of UDCA pre-treatment and response
- Safety profile of *nor*UDCA did not differ from placebo
- Based on these results a phase III trial in PSC is being planned

Trauner M, et. al. AASLD 2016.Abstract 210.

LANDSCAPE OF PSC CLINICAL TRIALS

- Bile acid mimetics
  - *nor*UDCA
- Farnesoid X agonist
  - OCA
  - GS-9674
- FGF19 Analogue
  - NGM 282
- Anti-Fibrotic
  - Simtuzumab (Monoclonal antibody against LOXL2)
- Anti-Adhesion
  - BTT1023 (VAP-1-blocking agent)
  - Vedolizumab (monoclonal antibody against α4/β7)
  - Cenicriviroc (CCR2 and CCR5 antagonist)
- Antimicrobials
  - Vancomycin

EMERGING THERAPIES PBC

- TITLE: Comparable Beneficial Effects of Beza- and Fenofibrate in PBC. An International Study in UDCA-treated individuals.

- 8 centers of the Global PBC Study Group

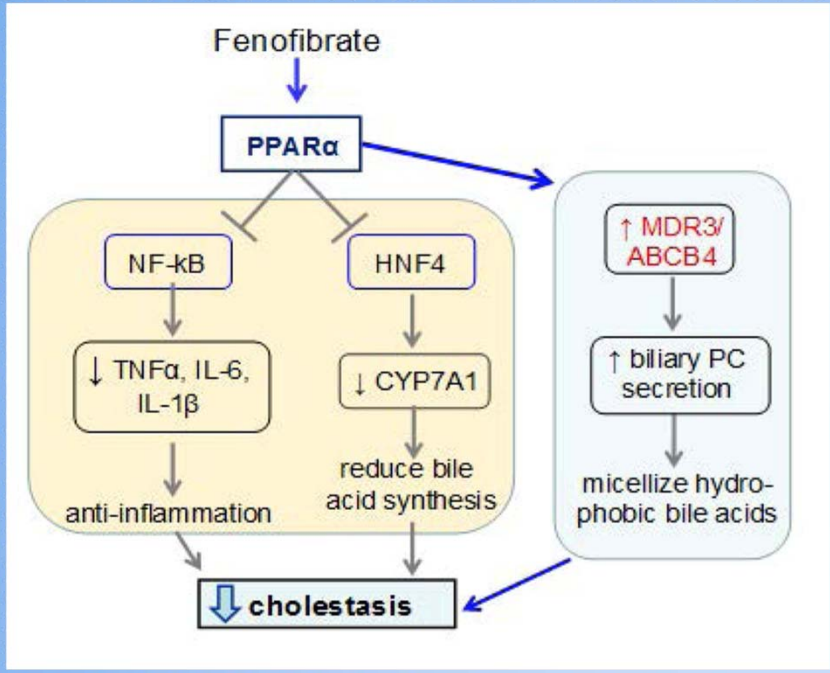
Harms MH, et al. AASLD 2016. Abstract 206.

BACKGROUND
FIBRATES

- Fenofibrate, a specific peroxisome proliferator-activated receptors [PPAR] alpha agonist and bezafibrate (a pan-PPAR agonist) have been shown in open pilot and short-term randomized trials to improve liver biochemistries and immunoglobulin (IgM) levels in PBC patients
  - Treatment-naïve
  - Incomplete biochemical responses to UDCA
- A phase 3 trial is ongoing in Europe to assess bezafibrate as an adjuvant therapy to UDCA (BEZURSO)

Yano K, et al. Am J Gastroenterol. 2002;97(4):1075.
Kurihara T, et al. Am J Gastroenterol. 2000;95(10):2990.
Nakai S, et al. Am J Gastroenterol. 2000;95(1):326.
Levy C, et al. Aliment Pharmacol Ther. 2011 Jan;33(2):235-42.

BACKGROUND FIBRATES



Proposed pathway of fenofibrate-mediated reduction of cholestasis via PPARαin the liver

Ligand	Human receptor EC_{50} (μM)		
	PPARα	PPARβ/δ	PPARγ
Wy-14,643	5	35	60
Clofibrate[a]	55	IA at 100	~500
Fenofibrate	30	IA at 100	300
Bezafibrate	50	20	60

[a] data is for the active metabolite, IA = inactive.

Potency of human PPAR agonists

Ghonem NS, et a. Hepatology. 2015 Aug;62(2):635-43.

AIM/METHOD

- To **evaluate fibrate treatment** in a large, international group of patients with **PBC with a suboptimal response to UDCA treatment.**

- METHODS
  - Retrospective, multi-center cohort study
  - Both feno- and bezafibrate treated patients
  - Laboratory results, disease complications and endpoints were recorded.
  - Exclusion criteria were FU < 3 months and autoimmune overlap syndrome.

Harms MH, et al. AASLD 2016. Abstract 206.

RESULTS (1)

- 211 patients with a median FU after fibrate initiation of 31 months (IQR12-51)
- 65% was treated with fenofibrate, and 35% with bezafibrate
- All patients had been treated with UDCA during a median time of 93 months (41-173)
- Patients were treated with fibrates during a median period of 27 months (11-48)
- Insufficient response to UDCA was the reason for starting fibrates in 97% of cases

Harms MH, et al. AASLD 2016. Abstract 206.

RESULTS (2)

- After 12 months, significant reductions compared to baseline of ALP ($p<.001$), ALT ($p<.001$) and AST ($p=.002$) were observed
  - Bilirubin did not significantly change ($p=.130$)
- 3- and 5-year transplant-free survival were 91% and 84%, respectively
- In multivariable analyses, stopping fibrates (time-dep HR5.2 (1.5-17.6)) and baseline AST (HR2.1; 1.4-3.1) are independent predictors of LTx/death
- Type of fibrate, duration of preceding UDCA treatment, age and sex were not associated with survival

Harms MH, et al. AASLD 2016. Abstract 206.

CONCLUSION

- This multi-centered study demonstrates that at 1 year, fibrates significantly reduce ALP, ALT and AST in patients with PBC with a suboptimal response to UDCA

- The effects of beza- and fenofibrate seem comparable

Harms MH, et al. AASLD 2016. Abstract 206.

FIBRATES: PHARMACOLOGY

	Fenofibrates	Bezafibrates
Elimination half-life	20-30 hrs.	1-2 hrs.
Time to peak	2-8 hrs.	3-4 hrs.
Excretion	Urine 60% (not removed by HD) Stool 25% Bile <20%	Urine 95% (no removed by HD) Stool 3%
Contraindication	Cr >2, GFR ≤30 Severe hepatic impairment PBC GB disease	Cr >1.5, GFR ≤ 60 Severe hepatic impairment PBC GB disease

drug-drug interactions

Drug	Concern	Recommendation
Warfarin	• Fenofibrate can prolong the PT/INR level	• Reduce anticoagulant dose • Monitor PT/INR frequently
Calcineurin Inhibitors (CI), i.e. cyclosporine, tacrolimus	• CI-fenofibrate interaction may increase risk of nephrotoxicity	• Use lowest effective dose • Monitor renal function frequently
HMG-CoA reductase inhibitors, i.e. statins	• Potential myalgias with older hydrophobic statins, i.e. lovastatin and gemfibrozil; No direct evidence of harm with fenofibrate	• Monitor patients on statins and fenofibrate for myalgias
Colchicine	• Potential rhabdomyolysis	• Prescribe with caution

Ghonem NS, et a. Hepatology. 2015 Aug;62(2):635-43.
Levy C, et al. Cholestatic Diseases SIG Webnar, June, 2016.

EMERGING THERAPIES
PBC

- TITLE: A phase 2 proof of concept study of MBX-8025 (PPAR-δagonist) in patients with PBC who are inadequate responders to UDCA

- An International Study

A. Steinberg M. et al. AASLD 2016. LB-9.

AIM/METHODS

- 12 week, double-blind, parallel, placebo-controlled, phase 2 study in patients with ALP >1.67 ULN despite UDCA for at least 12 months
- The study planned to randomize 75 patients to placebo, 50 or 200 mg/day of MBX-8025 +UDCA
- The primary outcome was ALP % change
- Safety was evaluated

A. Steinberg M. et al. AASLD 2016. LB-9.

RESULTS

- ALP decrease was significant compared to placebo (both $p<0.0001$), but there were no differences between 50 and 200 mg
- Three patients developed grade 3 ALT increases
  - One on 50, two on 200 mg
  - Increases were rapid, asymptomatic, not associated with increased bilirubin, considered drug-related, and fully reversible
- As the proof-of-concept was established, the study was discontinued half-way through recruitment
- No drug-induced pruritus observed
- Conclusion: benefit of MBX-8025 in patients affected with cholestasis should be further explored at lower doses

LANDSCAPE OF PBC CLINICAL TRIALS

- Approved agents
  - UDCA
  - FXR-agonist: obeticholic acid
- Fibrates
  - Phase III in Europe
- Glucocorticoids
  - UDCA plus budesonide (early disease) in Europe
- FGF-19 analog (NGM282)
  - Phase II
- ASBT inhibitors for Itch
  - LUM001 – Negative Result
  - GSK2330672- Positive Result
- Abatacept (a fusion protein composed of the Fc portion of IgG1 fused to CTLA4)
- TGR5 receptor agonists
- CAR and PXR agonists
- *Nor*UDCA

SURROGATE MARKERS OF DISEASE PROGRESSION IN PBC

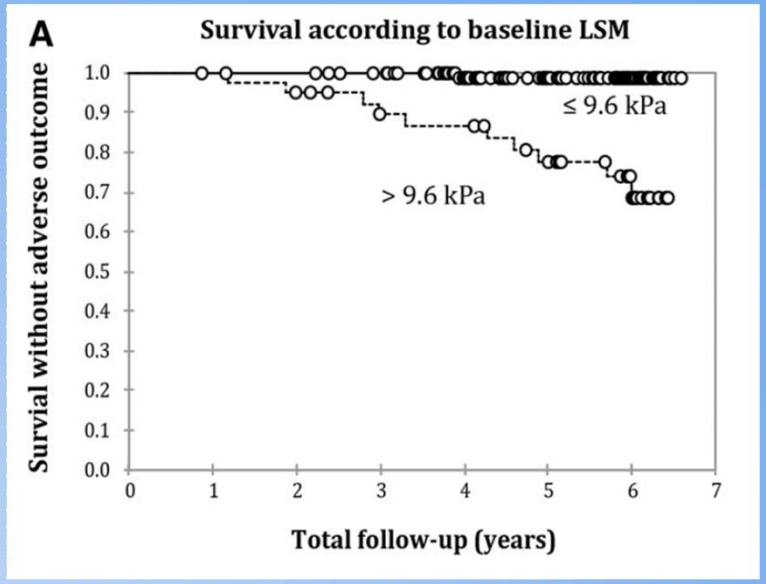
- TITLE: Relationships between **biochemical response to UDCA and progression of liver stiffness** as determined by FibroScan® in patients with PBC

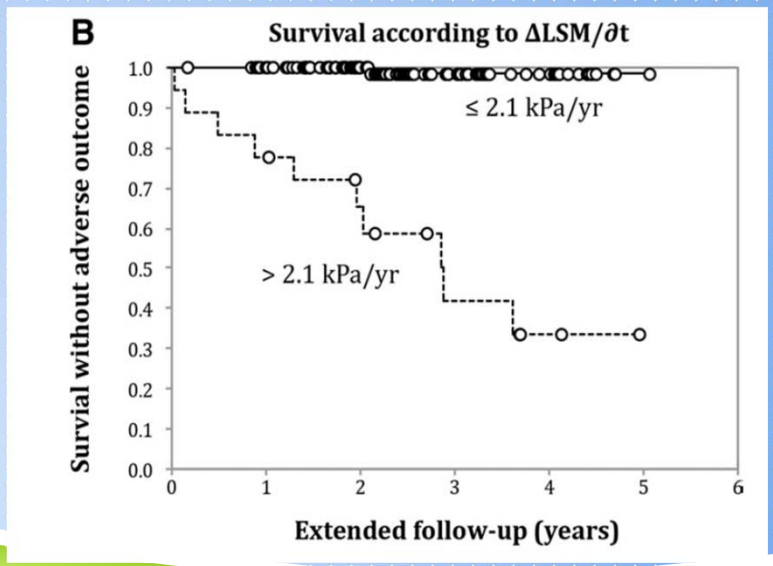
- French Group

Corpechot C, et al. AASLD 2016: Abstract 379.

BACKGROUND

- The biochemical response to UDCA therapy is recognized as the main predictor of liver transplantation (LT)-free survival in PBC
- This group previously has showed that liver stiffness (LS) >9.6 kPa or a progression in liver stiffness >2.1 kPa/year is associated with poorer outcomes in PBC
- LS as a potential surrogate end-point in clinical trials





Corpechot C, et al. Hepatology. 2012;56:198–208

METHOD

- A retrospective longitudinal study
- All PBC patients from a single center with at least 2 valid LSM performed within a minimum period of 12 months were included
- LSM was obtained using FibroScan® (Echosens, Paris, France)

RESULTS

- 176 patients treated with UDCA (13-15 mg/kg/d) for a median time of 5.0 yrs. from diagnosis to inclusion had 569 LSM over a total follow-up of 5.6 yrs.
- 23% of patients had advanced fibrosis or cirrhosis and 20% a suboptimal response to UDCA based on the Paris-I criteria
- The mean ΔLSM/t was 0.3 ± 3.2 kPa/yr
- ΔLSM/t was strongly associated with LT-free survival with an optimal predictive cutoff of > 1.4 kPa/yr
- In multivariate analysis, Paris-I criteria and albumin were the 2 parameters independently linked with ΔLSM/t

Corpechot C, et al. AASLD 2016: Abstract 379.

CONCLUSION

- Poor biochemical response to UDCA in PBC is associated with a higher rate of LSM progression
- There is a utility of monitoring LSM in PBC patients

Corpechot C, et al. AASLD 2016: Abstract 379.

LS MEASUREMENT RESPONSE TO TREATMENT IN PBC

- Title: Long-Term Effect of Obeticholic Acid (OCA) on Transient Elastography (TE) and AST to Platelet Ratio Index (APRI) in Patients with PBC

- Using data from the Phase 3 study investigating OCA in patients with PBC (POISE) (198 pts), along with data from the ongoing open-label extension (OLE) (193 pts)

- **They performed a post-hoc analysis to examine the effect of OCA on liver fibrosis as measured by APRI and TE**
  - TE was performed at sites where a Fibroscan device was available (~50% of sites)

- APRI >0.54 and liver stiffness >9.6 kPa or a progression in liver stiffness >2.1 kPa/year have been associated with poorer outcomes in PBC

Hirschfield G, et al. AASLD 2016. Abstract 209.
Trivedi PJ, et al. *J Hepatol*. 2014;60(6):1249-58.
Corpechot C, et al. *Hepatology*. 2012;56:198–208.

LONG TERM EFFECTS OF OCA ON APRI

Table 1. Mean Baseline and Change Values in Transient Elastography and APRI with OCA Treatment

Mean (SD)	Placebo ± UDCA	OCA 5-10 mg ± UDCA	OCA 10 mg ± UDCA
Baseline APRI	1.1 (1.0) n=73	1.1 (0.9) n=70	1.0 (0.8) n=72
Δ DB Month 12	0.1 (0.6) n=68	-0.2 (0.5)** n=60	-0.2 (0.5)** n=59
Baseline APRI > 0.54, Month 12 APRI≤ 0.54 n (%)	6 (9)	16 (27)	15 (25)
Δ OLE Month 12	-0.1 (0.5)* n=58	-0.2 (0.6)* n=59	-0.1 (0.7) n=55
Baseline TE (kPa)	12.7 (10.7) n=39	10.7 (8.6) n=35	11.4 (8.2) n=32
Δ DB Month 12	0.5 (3.0) n=34	0.6 (2.5) n=32	-0.3 (8.9) n=26
Δ OLE Month 12	0.9 (4.4) n=27	0.8 (6.9) n=29	-0.9 (7.4) n=26

*p<0.05, **p<0.01. P-value during DB for comparing active treatments to Placebo is obtained using an ANCOVA model with baseline value as a covariate and fixed effects for treatment and randomization strata factor. P-value during OLE for within group comparison was determined using a paired t-test. Values are Mean (SD) unless otherwise specified. 97% of patients completing the study enrolled in the OLE.

Hirschfield G, et al. AASLD 2016. Abstract 209.

LONG TERM EFFECTS OF OCA ON TE

Table 1. Mean Baseline and Change Values in Transient Elastography and APRI with OCA Treatment

Mean (SD)	Placebo ± UDCA	OCA 5-10 mg ± UDCA	OCA 10 mg ± UDCA
Baseline APRI	1.1 (1.0) n=73	1.1 (0.9) n=70	1.0 (0.8) n=72
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Hirschfield G, et al. AASLD 2016. Abstract 209.

LONG TERM EFFECTS OF OCA ON TE

- At baseline 7 (18%), 7 (20%), 6 (19%) of Placebo, OCA 5-10 mg, and OCA 10 mg patients had liver stiffness ≥16.9 kPa
  - During DB treatment, one Placebo patient and one OCA 5-10 mg patient progressed to a liver stiffness ≥16.9 kPa, but no patients in the OCA 10 mg group progressed
  - During DB treatment, only OCA-treated patients shifted below a liver stiffness of 16.9 kPa

LONG TERM EFFECTS OF OCA ON TE AND APRI

- These results suggest that OCA may improve long-term outcomes for patients with PSC

- Further studies are necessary to confirm the benefit of OCA in regards to reducing LS as measured by TE and the prognostic impact of reduced APRI with a larger number of patients

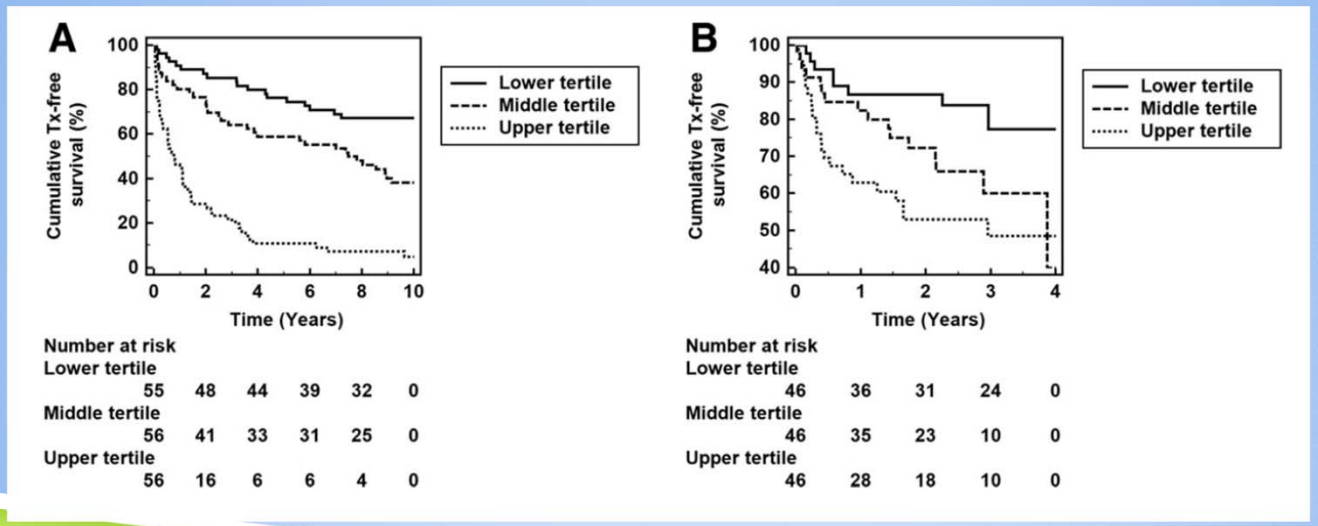
SURROGATE MARKERS OF DISEASE PROGRESSION PSC

- TITLE: Enhanced Liver Fibrosis (ELF) Test Predicts Transplant-free Survival in PSC

- European Multi-center Study (7 centers)

BACKGROUND

- ELF test is a direct marker of fibrosis based on three circulating markers of hepatic matrix metabolism that are expressed during early stages of collagen deposition in the liver:
  - Hyaluronic acid (HA)
  - Tissue inhibitor of metalloproteinases-1 (TIMP-1)
  - Propeptide of type III procollagen (PIIINP)
- ELF test was previously shown to predict outcome in PSC



(A) derivation panel and (B) validation panel (P = 0.005).

ELF test distinguished between mild and severe disease defined by clinical outcome (transplantation or death) in PSC with:

VM, et al. Gastroenterology 2004;127:1704-

AIM

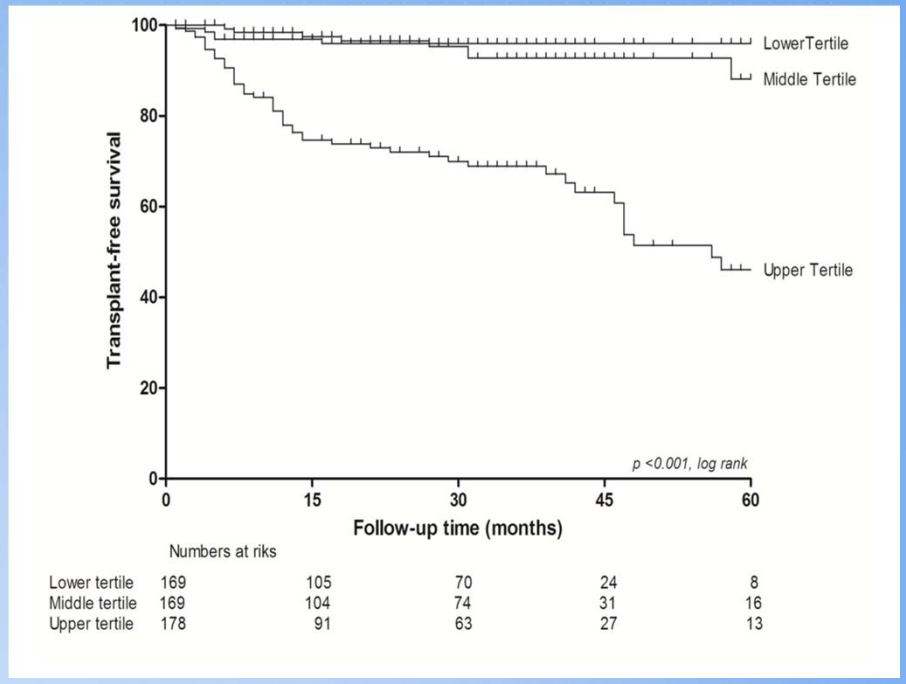
- The aim of this study was to validate the prognostic utility of the ELF test in an international, multicenter PSC cohort

ESULTS

4 PSC patients were included

F test levels were higher in
tients reaching an endpoint
edian 10.9 [IQR 9.8-12.1]) than in
ose censored (8.8 [IQR 8.0-9.8]);
0.001.

e risk of reaching the endpoint
as significantly different between
tients subdivided into tertiles of
F (p<0.001) (Figure 1)



UROC for the ELF test was 0.79
discriminating between PSC pt
th and without endpoint

CONCLUSION

- This data provides multi-center validation of the ELF test as a predictive test of clinical outcome in PSC
- Also provides robust evidence for the clinical utility of biomarkers for fibrosis in patients with PSC

AUTOIMMUNE HEPATITIS (AIH)

- TITLE: Mycophenolate Mofetil (MMF) in AIH Patients not Responsive or Intolerant to Standard Therapy: the Australian TAPESTRY study

- Background
  - Conventional therapy of AIH is corticosteroids with or without azathioprine
  - However 20% of patients do not respond or are intolerant to standard therapy

MMF FOR AIH

- AIM/Method
  - To evaluated the efficacy and safety of MMF in AIH patients who had failed or were intolerant to corticosteroids with or without azathioprine
  - A retrospective study
  - Patients were recruited from 16 liver clinics across Australia

MMF FOR AIH
RESULT

- A total of 96 patients (mean age 45.3 yrs, females 86.5%, Caucasian 53%, cirrhosis 19.8%) received treatment with MMF for AIH (95 in combination with corticosteroids)
- The majority (73%) had received prior combination therapy with corticosteroids plus azathioprine/6-mercaptopurine
- The indication for MMF was non-response in 43% and intolerance to standard therapy in 53%
- The median starting and maximal doses of MMF received was 1gm/d and 2gm/d respectively; the median treatment duration was 31.9 months

RESULTS

	Biochemical remission (BR) n(%)	Median time to induce BR (Weeks)	Relapse n(%)	Incomplete response n(%)	Treatment failure n(%)
ll patients N=96	44(45%)	11	8(18%)		
reated for n-response N=40	17(42%)	12		8(20%)	3(7.5%)
reated for tolerance N=49	27(55%)			4(8%)	1(2%)

RESULTS

- 8 patients required dose-reduction and 16 discontinued MMF mainly due to lack of efficacy (n=6) or intolerance (n=6)
- Serious adverse events occurred in 3 patients (1 death, 2 hospitalizations)
- There were 23 significant complications
  - GI toxicity (n=8)
  - Infection (n=5)
  - Cytopenias (n=3)
  - Neuropsychiatric (n=3)
  - Skin cancer (n=2), and
  - Lymphoproliferative disorder (n=1)

CONCLUSION

- Treatment with MMF combined with corticosteroids in AIH patients who fail to respond or are intolerant to standard therapy is moderately effective achieving an overall remission rate of around 50% including 43% in non-responders to standard therapy.

- MMF appears relatively safe and well tolerated with the main side-effects being GI toxicity, infection, and cytopenias

SUMMARY

- The landscape of drug development in cholestasic liver diseases is promising
- Development/validation of surrogate markers of clinical outcomes in PSC/PBC in crucial to facilitate therapeutic development for these orphan diseases
- MMF is effective for AIH patients not-responsive to conventional therapies. However studies are needed to better understand this cohort and develop therapeutic agents targeting this difficult patient population

THANK YOU

- Micheal Trauner, MD
- Gideon Hirshfield, MD
- Chris Bowlus, MD