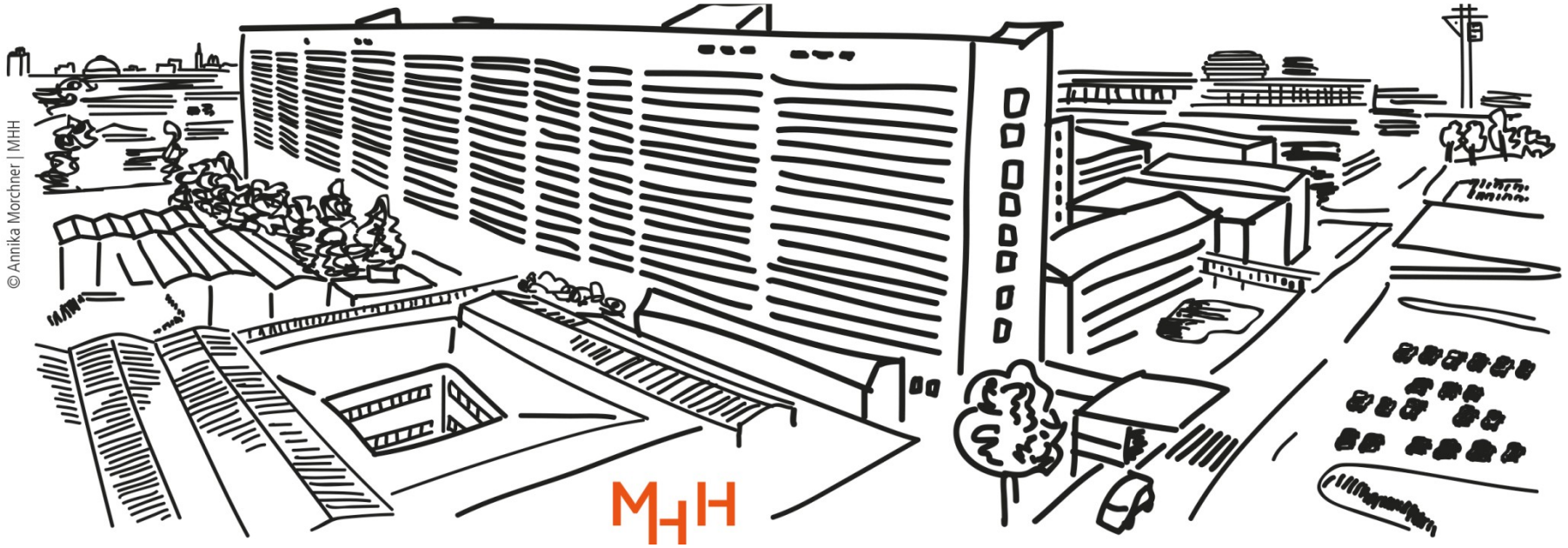
# The future of autoimmune liver diseases




**MICHAEL MANNS**

**Hannover Medical School, Germany**

**PHC 2020, Paris, 13 January 2020**

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**Elmar Jaeckel**



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# CONFLICTS OF INTEREST

**Falk Pharma, Freiburg, Germany**

**Gilead Sciences, Foster City, USA**

**Intercept**

**Novartis, Basel , Switzerland**

**Roche, Basel, Switzerland**

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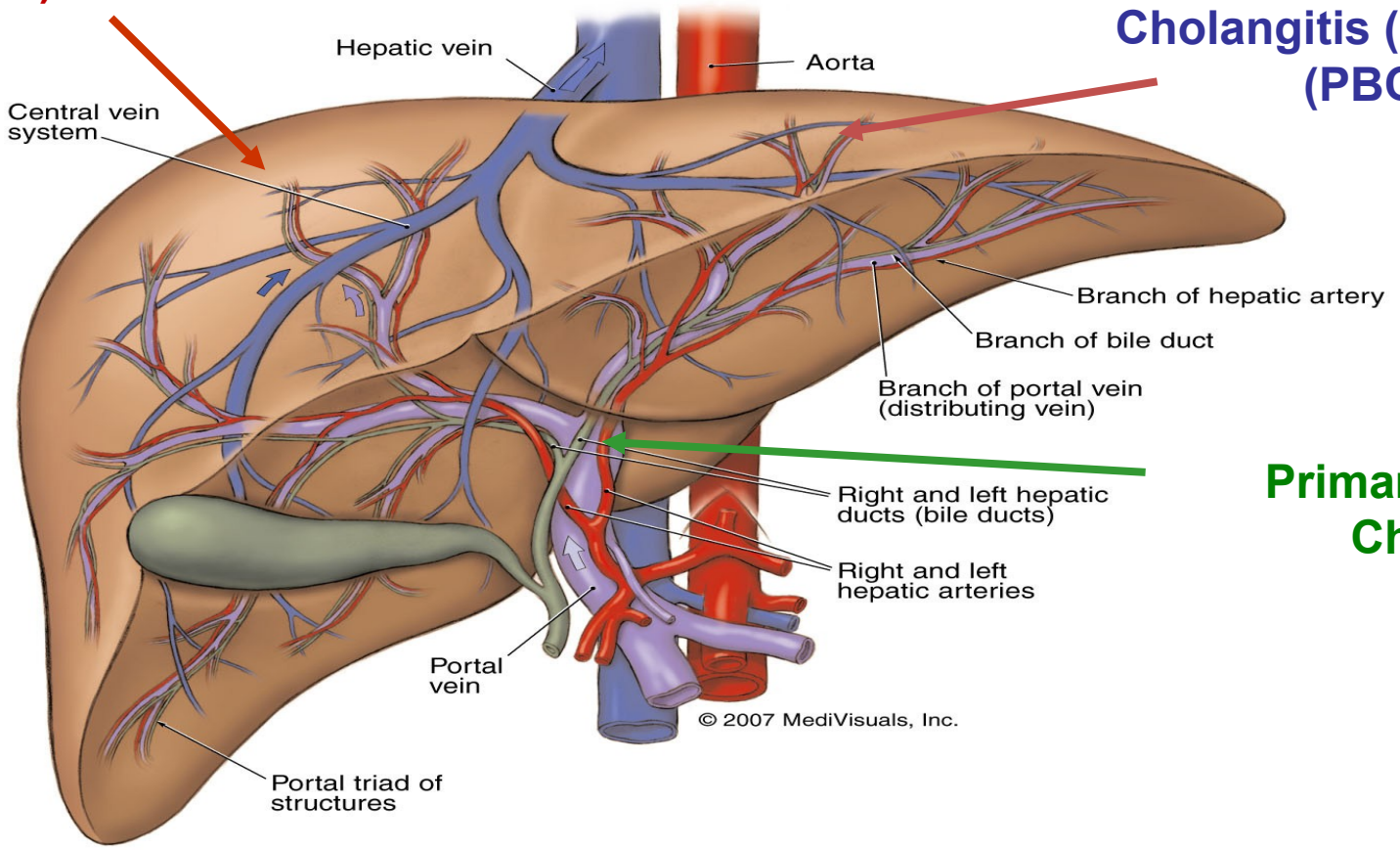
# Autoimmune Liver Diseases

**Autoimmune hepatitis (AIH)**

**Primary Biliary Cholangitis (Cirrhosis) (PBC)**




**Primary Sclerosing Cholangitis (PSC)**

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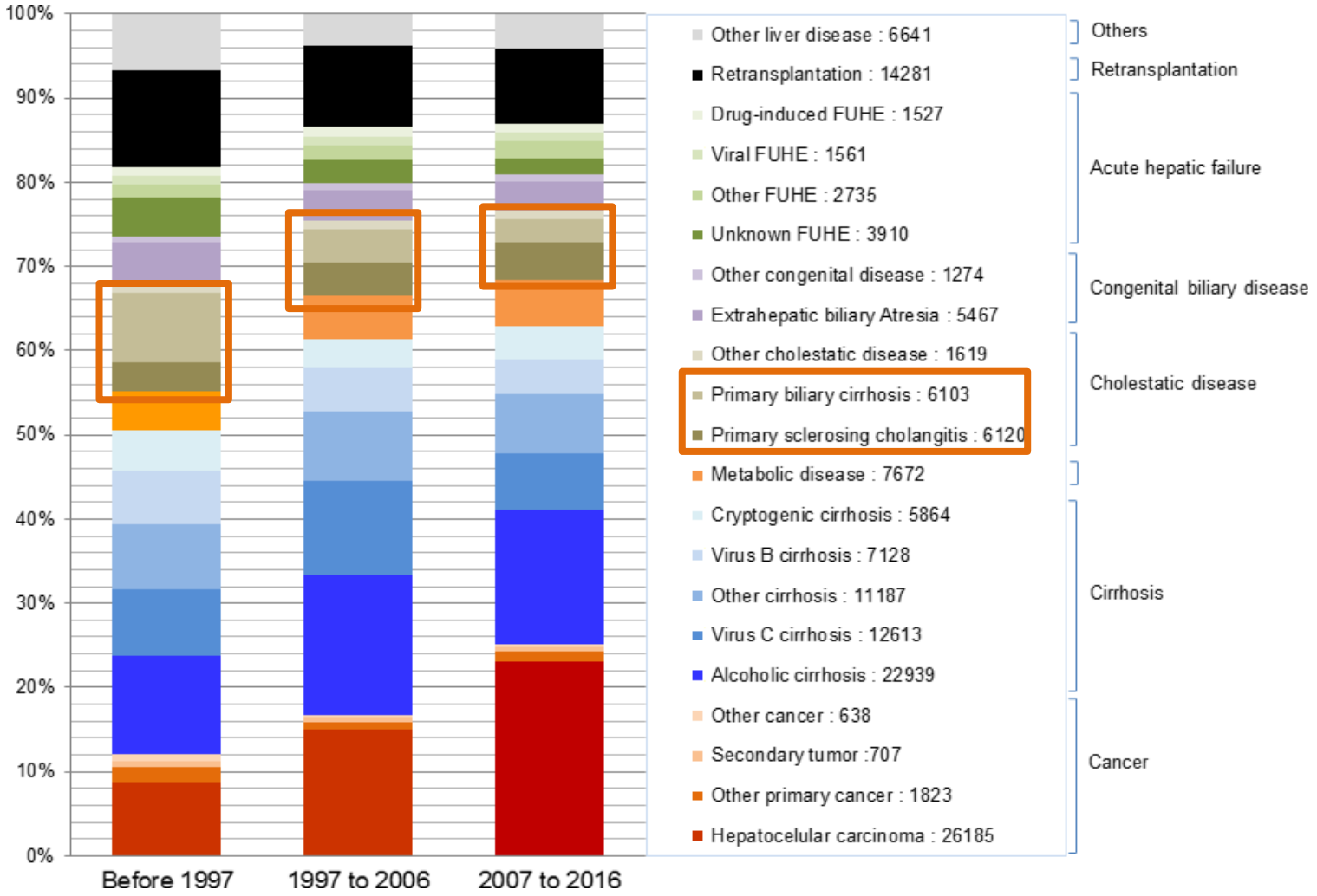
# 2018 Annual Report of the European Liver Transplant Registry (ELTR)




Adam et al. Transplant International 2018; 31: 1293–1317

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# Primary Biliary Cholangitis

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13.01.2020

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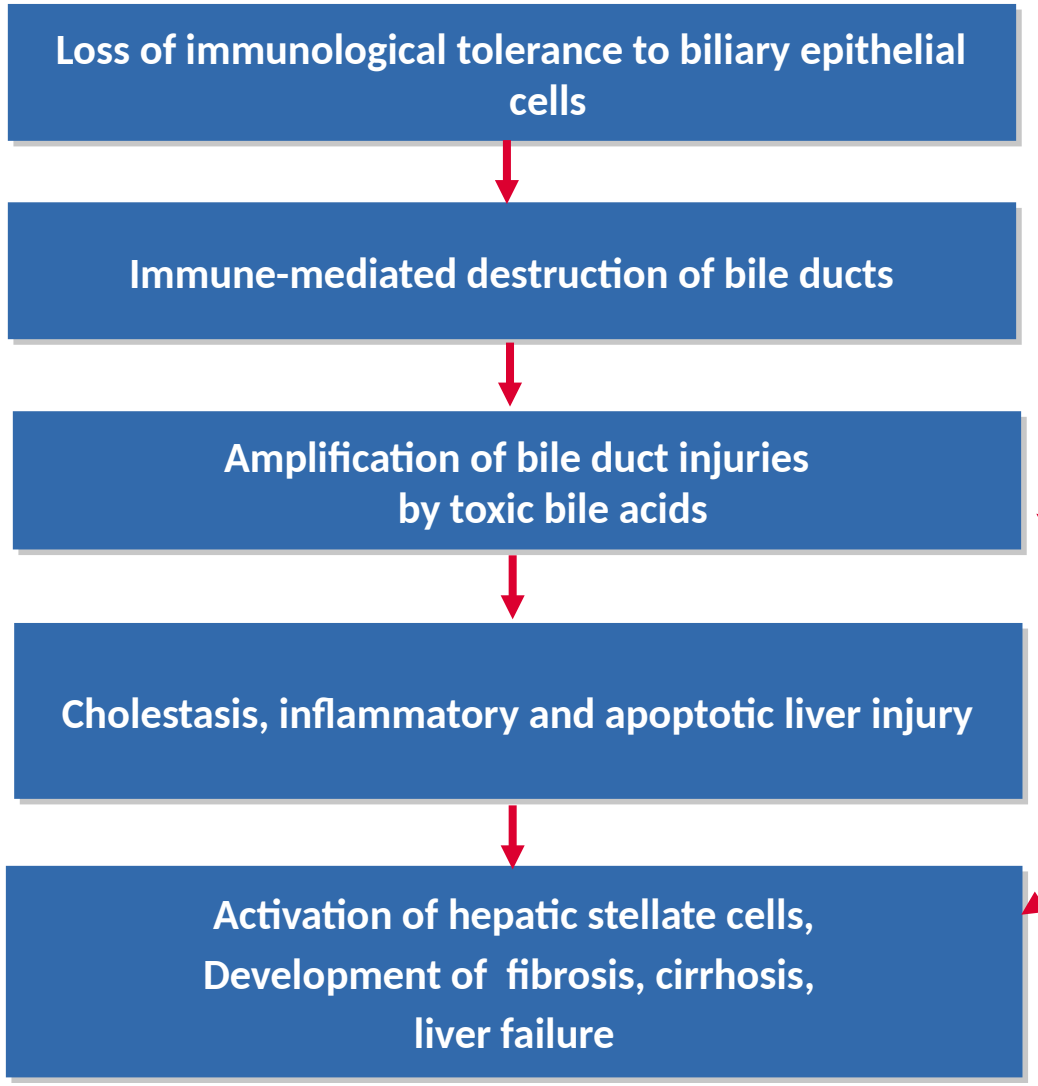
# Pathomechanisms of PBC

Modified according to U. Beuers




## First Line Therapy

**Ursodesoxycholic acid (13-15 mg/kgBW/day)**

Hydrophilic bile acids ↑
Intestinal resorption of toxic bile acids ↓
Choleresis ↑
Inflammation, apoptosis ↓

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# Defining Inadequate Response to UDCA Treatment

| Score [References] | Time (months) | Treatment Failure |
|---|---|---|
| Barcelona<br>[Pares A, Gastroenterol 2006] | 12 | Decrease in ALP ≤ 40% and<br>ALP ≥ 1 x ULN |
| Rotterdam<br>[Kuiper EM, Gastroenterol 2009] | 12 | bilirubin ≥ 1 x ULN<br>and/or albumin < 1 x ULN |
| Paris-I<br>[Corpechot C, Hepatology 2008] | 12 | ALP ≥ 3 x ULN or<br>AST ≥ 2 x ULN,<br>or bilirubin >1 mg/dL |
| Paris-II<br>[Corpechot C, J Hepatol 2011] | 12<br>(for early histological stages) | ALP ≥ 1,5 x ULN or<br>AST ≥1,5 x ULN,<br>or bilirubin > 1 mg/dL |
| Toronto<br>[Kumagi T, Am J Gastroenterol 2010] | 24 | ALP > 1,67 x ULN |
| UK-PBC-Risk Score<br>[Carbone M, Hepatology 2016] | 12 | Albumin and platelet count<br>at baseline<br>Bilirubin, ALP, AST or ALT<br>at 12 mo |
| GLOBE-Score<br>[Lammers WJ, Gastroenterol 2015] | 12 | Age at baseline<br>Bilirubin, ALP, albumin,<br>platelet count at 12 mo |

**25 - 50% UDCA treatment failure (depending on which definition was used)**

**EASL CPG J Hepatol 2017**

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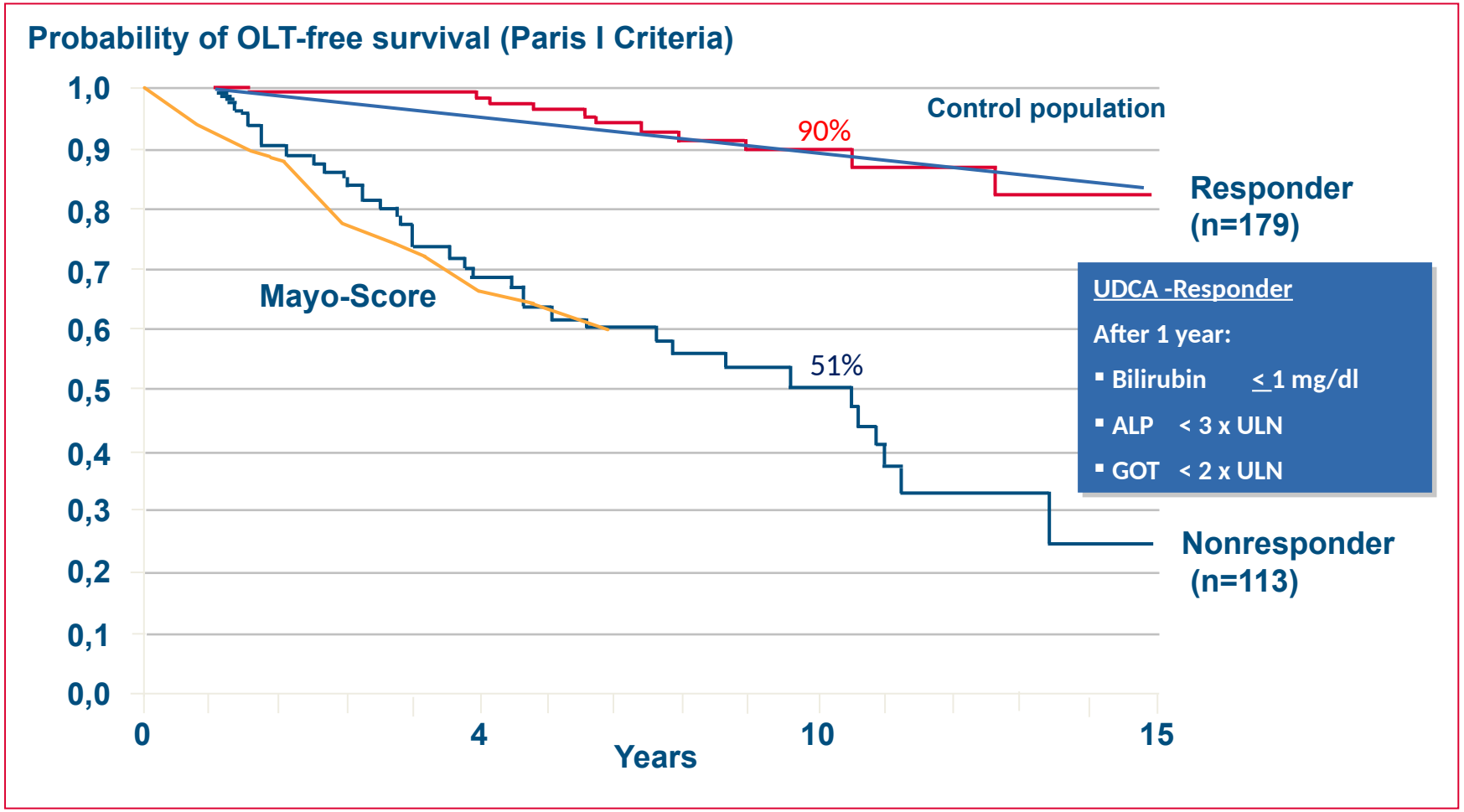
**EASL CPG J Hepatol 2017**

# Long-Term Survival of PBC Patients with Biochemical Response to UDCA




Corpechot et al. *Hepatology* 2008;48:871

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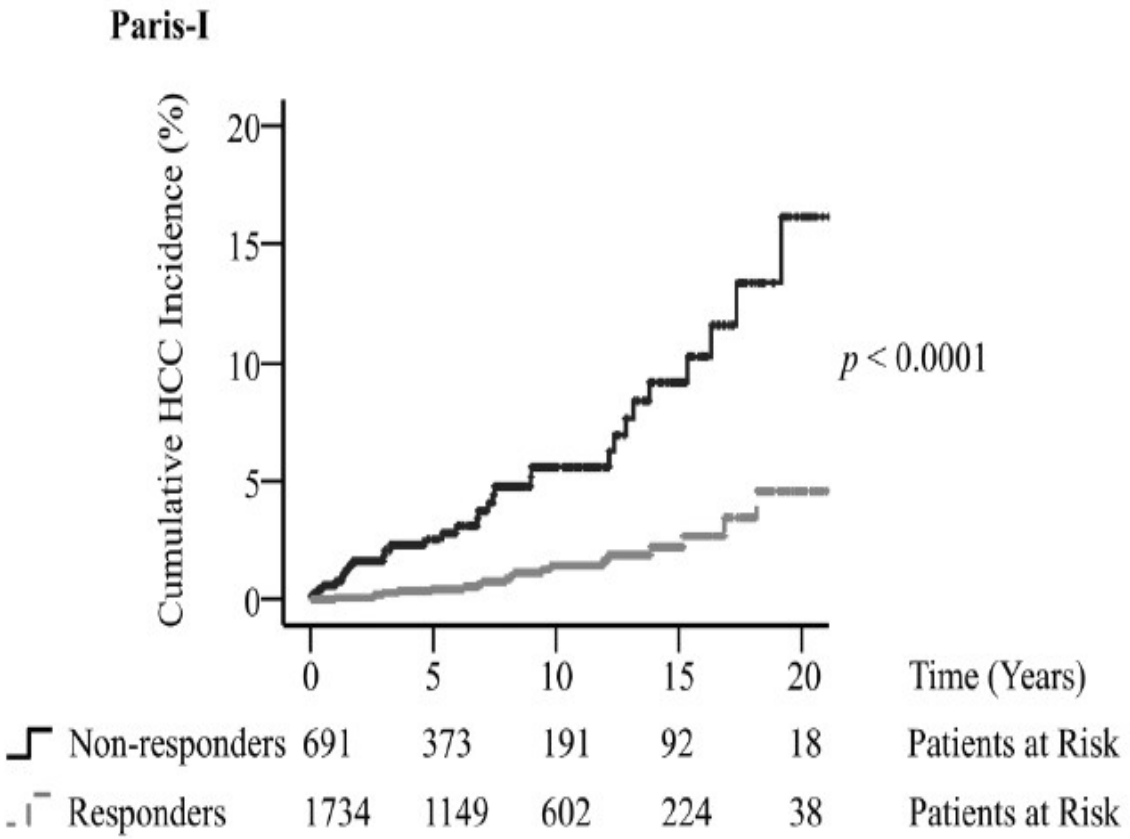
# UDCA Treatment Failure – Increased Risk for HCC Development




Trivedi PJ et al., Gut 2016; 65:321-329

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# POISE (Phase 3) Trial: Obeticholic Acid (OCA) vs. Placebo in PBC Patients with Inadequate Response to UDCA

Primary endpoint at 12 months:

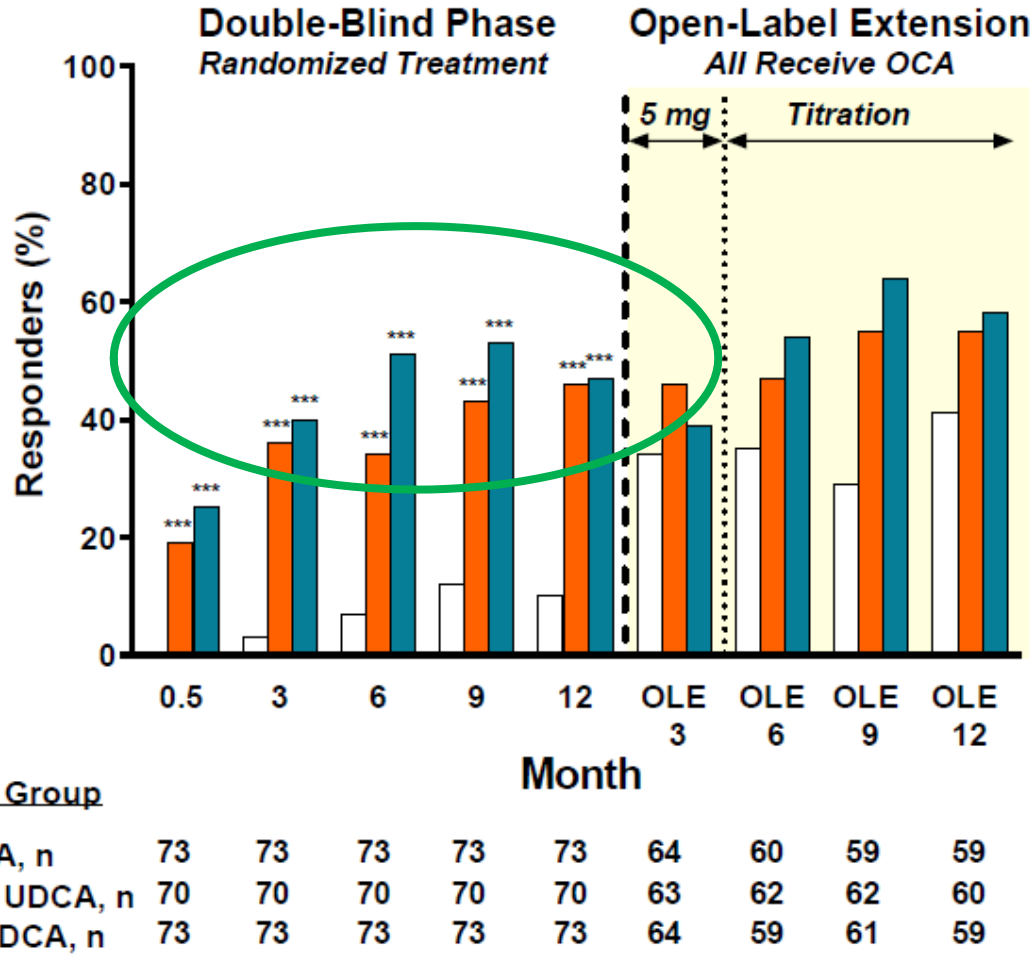
OCA 5-10 mg: 46%
OCA 10 mg: 47%
Placebo: 10%

Side effects:

Dose-dependent increase of pruritus

(leading to OCA discontinuation in 1-10%)

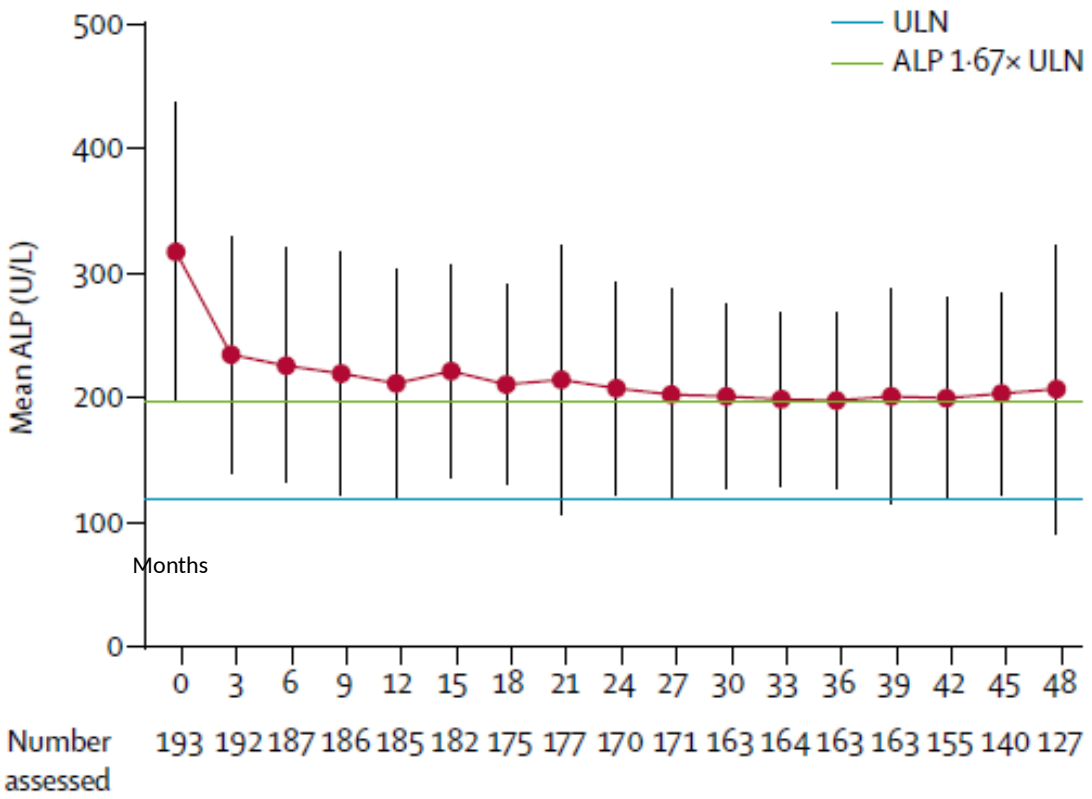
LDL-increase (long-term cardiovascular risk?)




Nevens F, New Engl J Med 2016

# OCA Therapy for PBC – Long term results

## OCA Add-on UDCA (POISE-Study, OLE) (3 years results)




Response rates

(AP<1.67xULN, AP decrease ≥15%, normal bilirubin)

Month 24: 53%

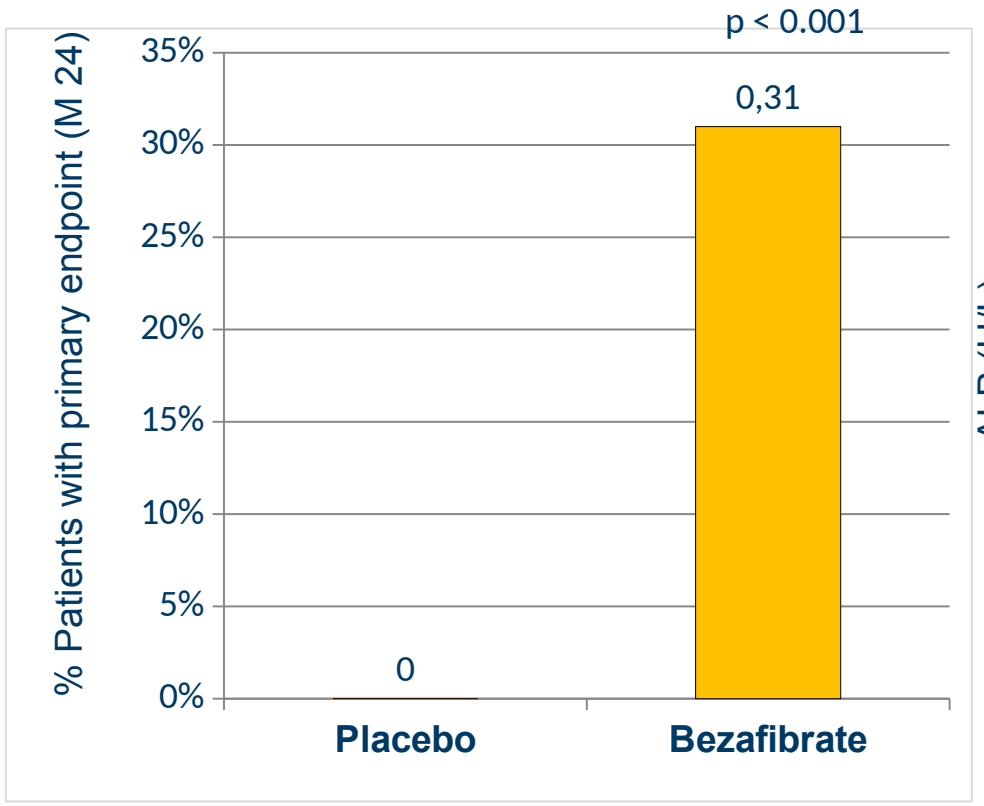
Month 48: 51%

**Trauner M et al., Lancet Gastroenterol Hepatol 2019**

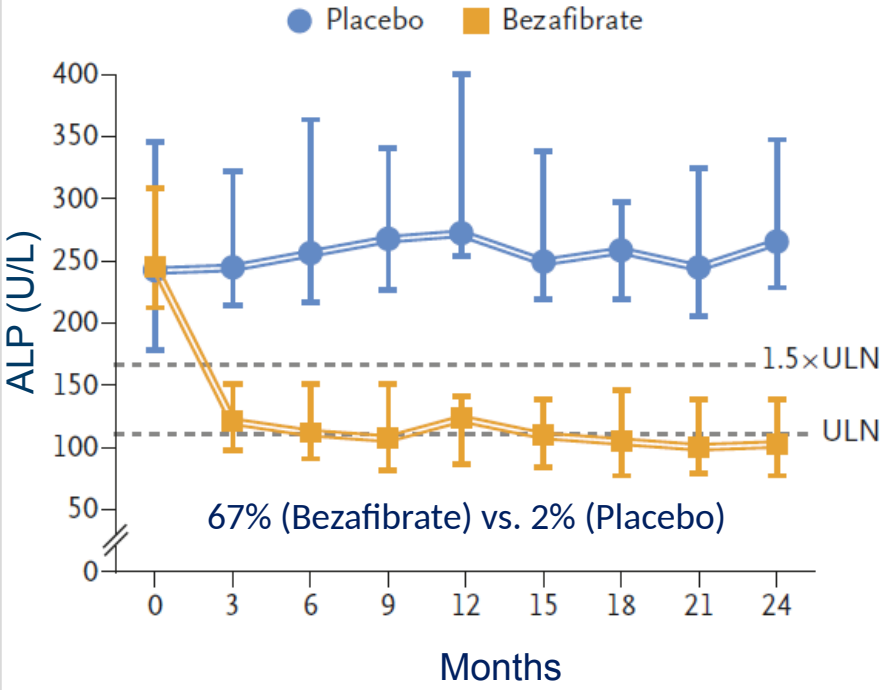
# BEZURSO (Phase 3) Trial: Bezafibrate vs. Placebo in PBC Patients with Inadequate Response to UDCA

## Primary endpoint: Complete biochemical response at month 24

*(Normalization of Bilirubin, AP, AST, ALT, Albumin, Prothrombin-Index)*




## Secondary endpoint: Normalization of AP at month 24




Carpechot C et al. N Engl J Med 2018;378(23):2171-81.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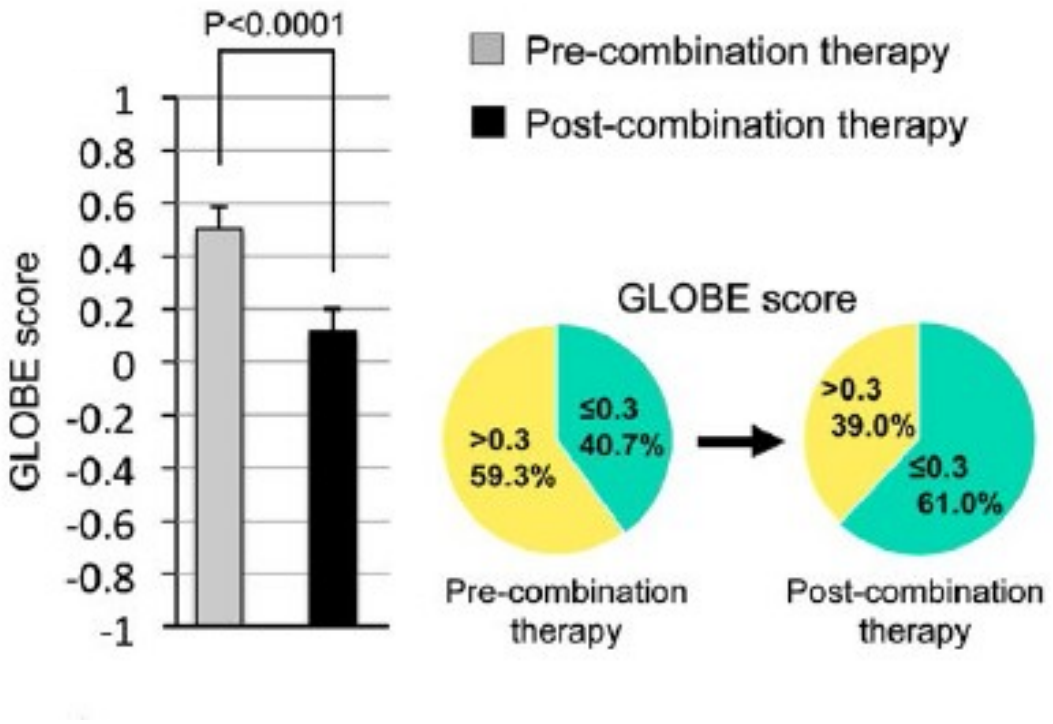
# Improvement of GLOBE Score by the Combination of UDCA with Bezafibrate in PBC




**Honda A et al. Hepatology 2019**

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# Addition of Bezafibrate to OCA +/- UDCA

Add on Bezafibrate (400 mg/d) after 5 y OCA (5/10 mg/d) +/- UDCA in 11 POISE study patients
Bezafibrate termination in 2/11 patients due to myalgia

- After 6 month triple treatment, ALP further decreased in 100% of patients ($p < 0.001$) and bilirubin decreased in 67% of patients ($p=0.184$)
- ALP was normal in 4/9 patients and bilirubin was normal in 8/9 patients, reaching the primary endpoint in 44% of the patients

**Table 1. Biochemical parameters (Median [IQR])**

| | start OCA (n = 11) | 6 m OCA (n = 11) | 4 – 5 y OCA (n = 11) | 6 m OCA + bezafibrate (n = 9) |
|---|---|---|---|---|
| ALP (U/L) | 315.0 [275.0 - 408.4] | 233.2 [194.4 - 259.4] | 190.2 [157.4 - 252.0] | 94.0 [90.0 - 143.5] |
| BILI (µMOL/L) | 7.7 [6.8 - 20.9] | 8.6 [5.8 - 18.0] | 7.7 [6.8 - 14.7] | 6.8 [5.0 - 10.5] |
| AST (U/L) | 37.2 [27.9 - 67.9] | 35.9 [23.8 - 69.0] | 29.3 [26.3 - 47.8] | 37.0 [27.5 - 48.5] |
| ALT (U/L) | 45.6 [27.2 - 67.8] | 29.3 [17.4 - 46.0] | 21.9 [15.5 - 32.0] | 27.0 [19.5 - 37.0] |
| GGT (U/L) | 274.7 [97.3 - 397.7] | 71.0 [52.1 - 189.9] | 37.2 [27.6 - 87.8] | 32.0 [26.5 - 103.0] |

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**Smets L et al., EASL 2019**

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**Smets L et al., EASL 2019**

# Clinical Trials in PBC

- Seladelpar (PPAR-δ Agonist; CYMABAY)
- Elafibranor (PPAR-α/δ Agonist; GENFIT)
- Cilofexor (Non-steroidal / Non bile acid FXR-Agonists; GILEAD, NOVARTIS)
- FGF-19 Agonist (NGM282; NGMBio)

# Seladelpar (PPAR-δ Agonist; CYMABAY)

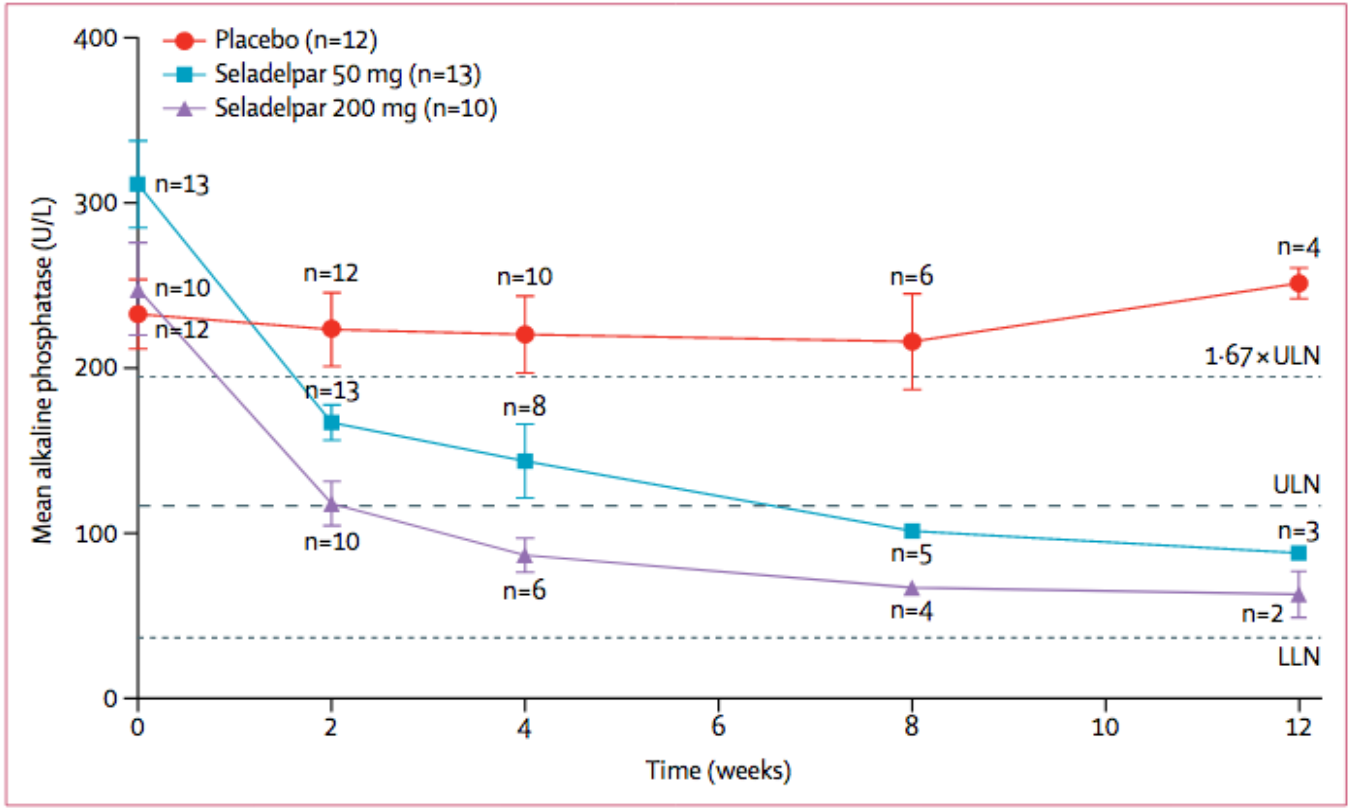
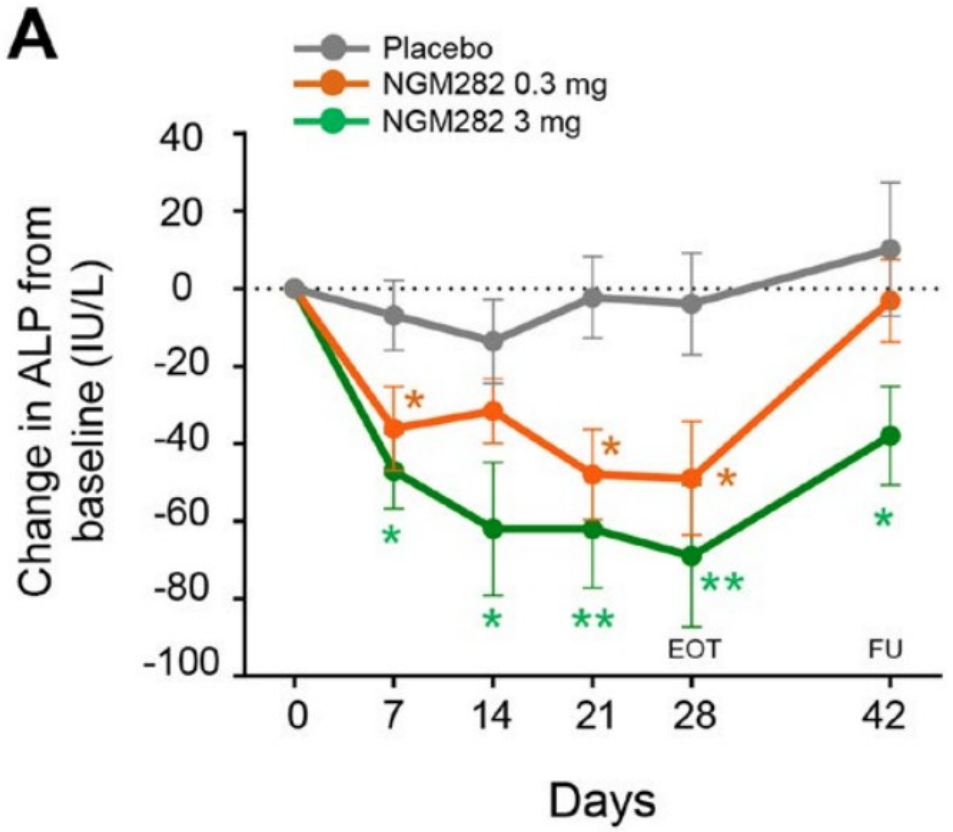



***Figure 3:*** **Mean changes in alkaline phosphatase over 12 weeks for each treatment group**
ULN=upper limit of normal. LLN=lower limit of normal. Bars are SE.

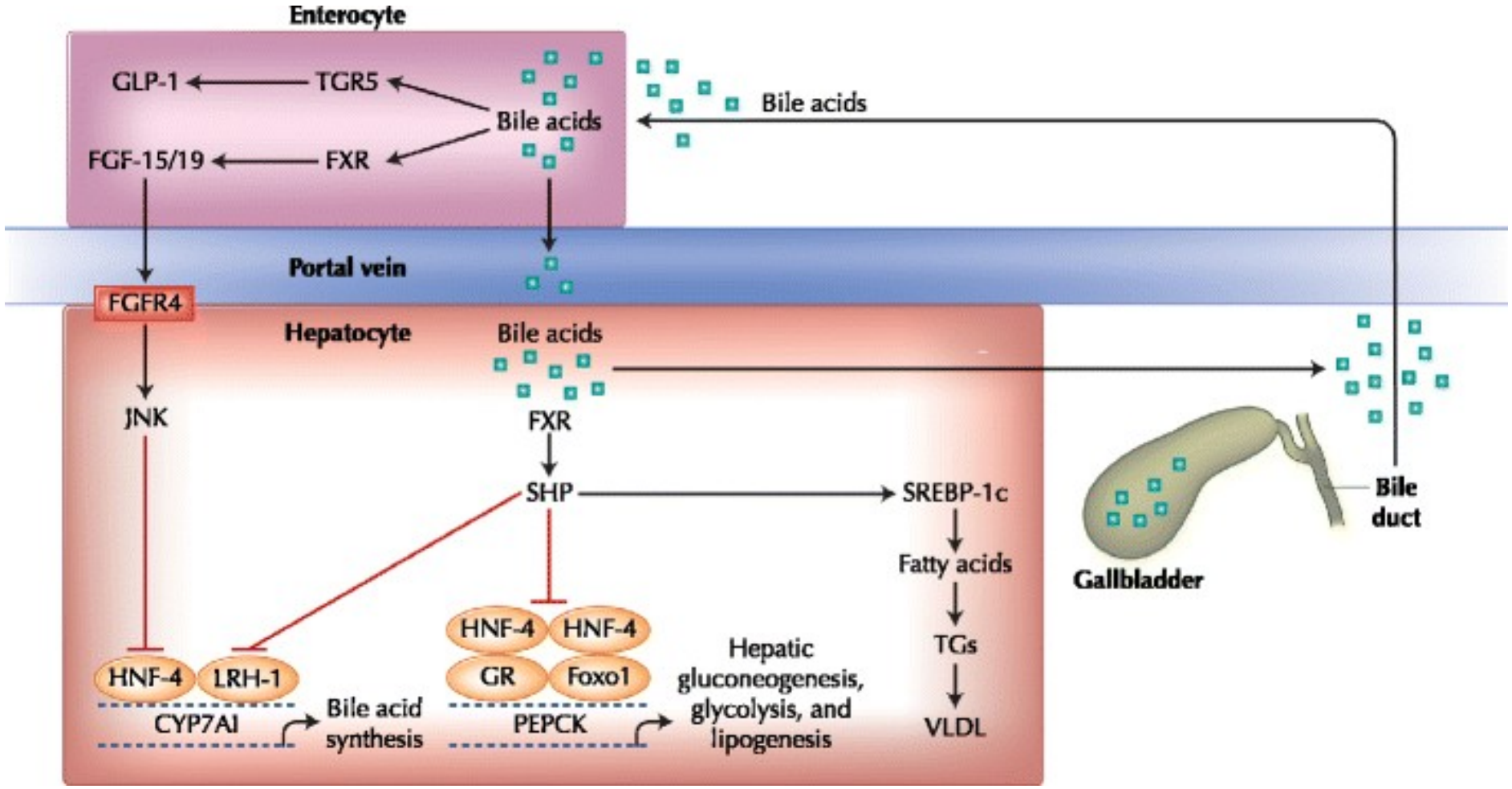

Jones, D., Boudes, P. F., Swain, M. G., Bowlus, C. L., Galambos, M. R., Bacon, B. R., … Hirschfield, G. M. (2017). *Seladelpar (MBX-8025), a selective PPAR-δ agonist, in patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid: a double-blind, randomised, placebo-controlled, phase 2, proof-of-concept study. The Lancet Gastroenterology & Hepatology, 2(10), 716–726.* doi:10.1016/s2468-1253(17)30246-7

# FGF-19 Agonist (NGM282; NGMBio)




Mayo MJ, Wigg AJ, Leggett BA, et al. NGM 282 for Treatment of Patients With Primary Biliary Cholangitis: A Multicenter, Randomized, Double–Blind, Placebo–Controlled Trial . *Hepatol Commun*. 2018. doi:10.1002/hep4.1209

# Role of FGF15/19 as Therapeutic Target




Staels, B., Handelsman, Y. & Fonseca, V. Curr Diab Rep (2010) 10: 70

# Current therapeutic trials for PBC

| | | |
|---|---|---|
| Mesenchymal stem cell transplantation for refractory primary biliary cholangitis | RCT, assessment of change of ALP after mesenchymal stem cell transplantation vs. placebo | ? |
| Study to evaluate safety, tolerability and efficacy of saroglitazar Mg in patients with primary biliary cholangitis (EPICS) | Phase 2 placebo controlled study measuring change in ALP levels after 16 weeks of treatment | PPARα/γ-agonism |
| Clinical Trial on the effect of the sublimated mare milk supplement on primary biliary cholangitis | Changes of liver chemistry, histology, asthenia and hepatic encephalopathy in PBC patients after 4 months of treatment | ? |
| ENHANCE: Seladelpar in Subjects with primary biliary cholangitis (PBC) and an inadequate response to or an intolerance to urseodycholic acid (UDCA) | Phase 3 study to determine safety and efficacy of Seladelpar against placebo; composite endpoint of change in ALP and total bilirubin within 12 months | PPARδ-agonism |
| Mindfulness - based intervention in the treatment of fatigue in patients with primary biliary cholangitis | Change in fatigue severity over 16 weeks of mindfulness - based intervention | Behavioral intervention |
| A study to assess the safety, tolerability, pharmacokinetics and efficacy of EDP-305 in subjects with primary biliary cholangitis | Phase 2 to measure proportion of subjects with at least 20% reduction in ALP within 12 weeks of treatment | small molecule FXR agonist |
| Safety, Tolerability of OP-724 in patients with primary biliary cholangitis (Phase I) | Phase 1 study looking primarily for occurence of adverse events | CBP/beta-catenin antagonist (potentially antifibrotic) |
| Combination antiretroviral therapy (cART) for PBC | ALP change > 10 % within 12 months of tenofovir/raltegravir/emtricitabine treatment (Phase 2) | |
| Curative effect observation of UDCA combined probiotics therapy in PBC of poor response to UDCA (CEOBOFUCPTIP) | Change of fecal flora after 6 month and biochemical response | |
| Phase 4 study of obeticholic acid evaluating clinical outcomes in patients with primary biliary cholangitis (COBALT) | Study long term outcomes of OCA treatment (death, LTX, hospitalization) | FXR-agonist |
| Study of OCA evaluating pharmacokinetics and safety in patients with PBC and hepatic impairment | Safety study Phase 4 in patients with PBC and hepatic malfunction | FXR-agonist |
| Study to evaluate the safety and efficacy of oral CR845 (Difelikefalin) in patients with primary biliary cholangitis and moderate-to-severe pruritus | Phase 2 trial to evaluate change in itching measured by worst itching intensity numeric rating scale (WI-NRS) within 16 weeks of treatment | κ-opioid receptor agonist |
| Dose Response Study of GSK2330672 for the Treatment of Pruritus in Patients With Primary Biliary Cholangitis | Phase 2 study to evaluate the change in itching measured by WI-NRS within 16 weeks of treatment | ASBT(apical sodium-dependent bile acid transporter) inhibitor |

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# Primary Sclerosing Cholangitis

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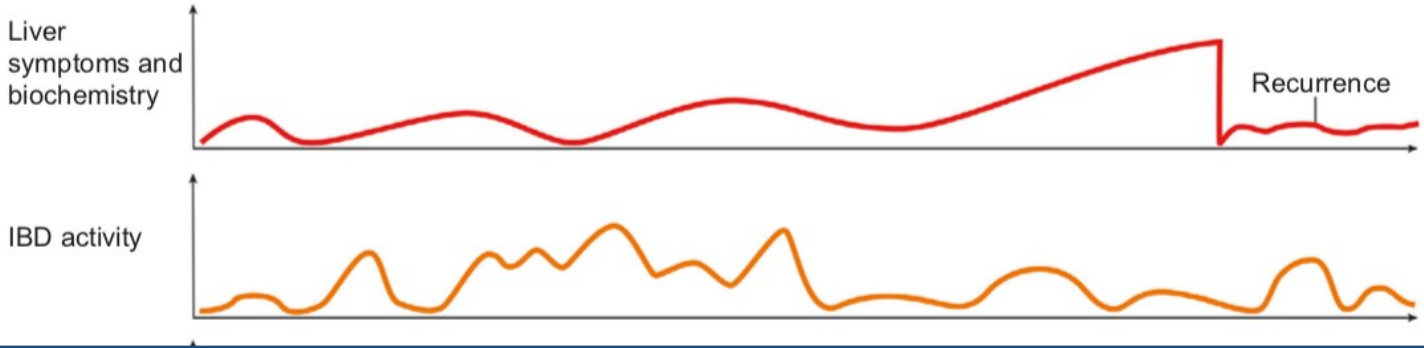
# PSC remains one of the greatest unmet needs in hepatology




## THE BLACK BOX OF HEPATOLOGY

- ✓ un-defined aetiology and ill defined pathogenesis.
- ✓ Risk of malignancy
- ✓ Critical absence of medical therapies.
- ✓ Liver transplantation remains the only life-saving intervention for patients.

Karlsen TH et al. Journal of Hepatology 2017

# What´s new about the pathophysiology of PSC ?

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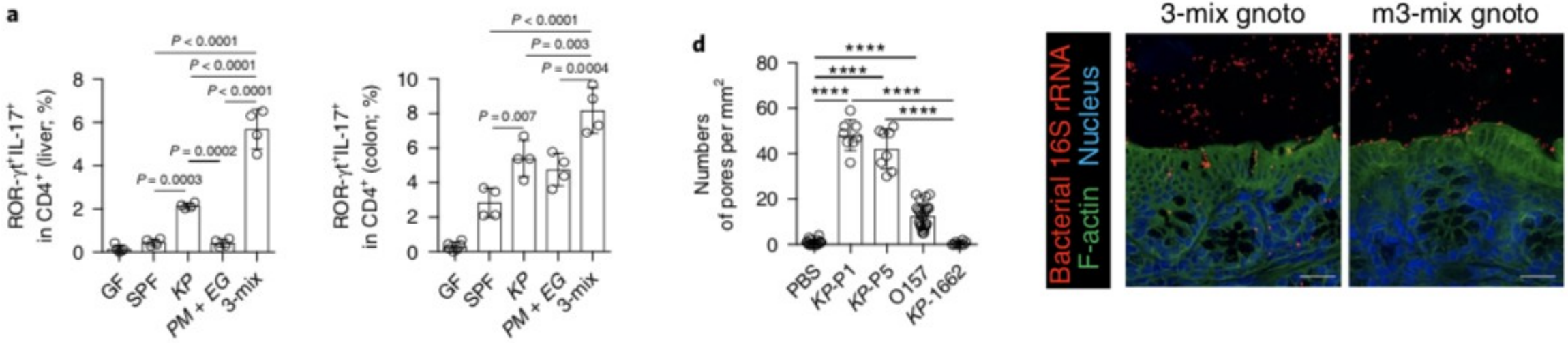
13.01.2020

# Gut pathobionts underlie intestinal barrier dysfunction and liver T helper 17 cell immune response in PSC




- ✓ This study highlights the role of pathobionts in intestinal barrier dysfunction and liver inflammation.
- ✓ *K.pneumoniae*, *P.mirabilis* and *E.gallinarum* were found to be prevalent in patients with PSC and responsible for bacterial translocation and subsequent hepatobiliary inflammation in the gnotobiotic mouse models.
- ✓ PSC-derived *K. pneumoniae* possess epithelial-damaging abilities that contribute to bacterial translocation.
- ✓ The 3-mix bacteria cooperatively promote the hepatobiliary disease progression through the TH17 response.

Nakamoto N et al. Nature Microbiology 2019

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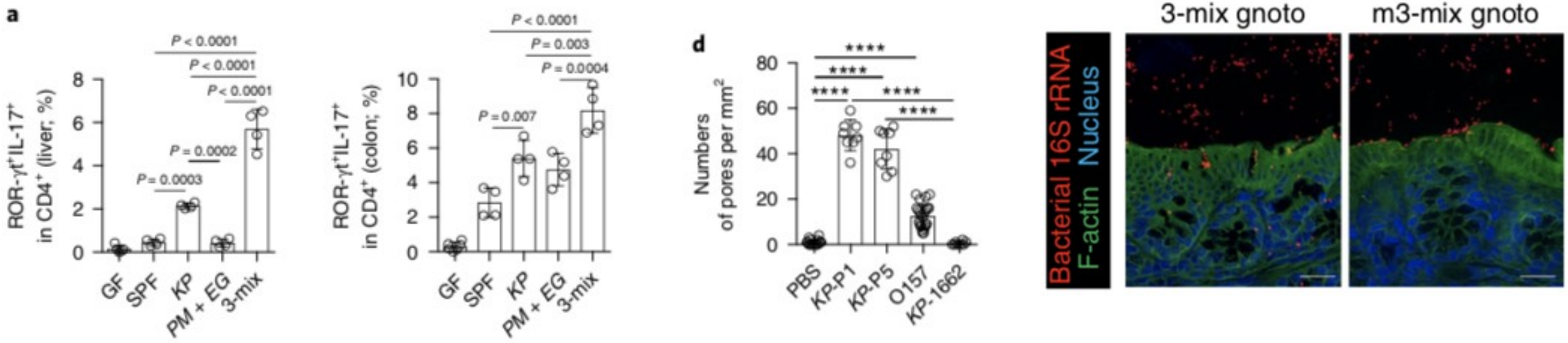


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Nakamoto N et al. Nature Microbiology 2019

# What´s new about future therapies for PSC ?

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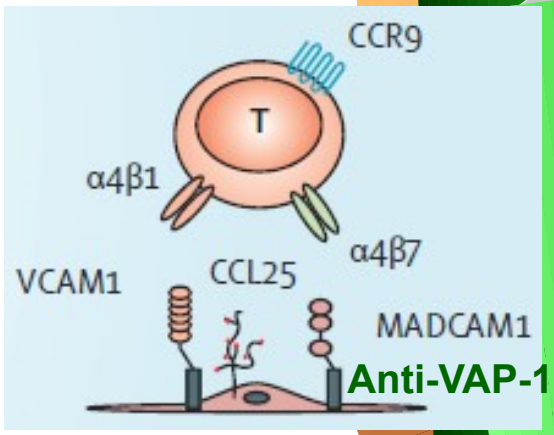
# Novel Therapeutic Strategies in PSC- Overview
# Candidates for Recent & Future Clinical Trials

Cenicriviroc

Etrolizumab
Vedolizumab

norUDCA

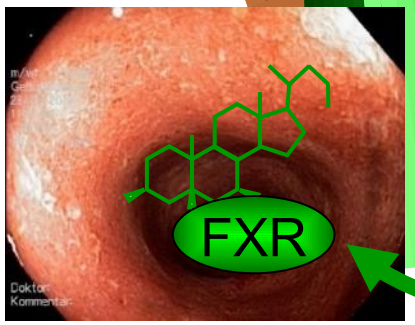



*Lancet* 2013;382:1590

PPAR
FXR
RAR

Simtuzumab

Antibiotics
(Vancomycin,
Minocyclin,
Metronidazol)

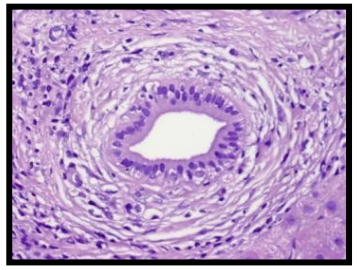



Colitis (~75%)

FXR

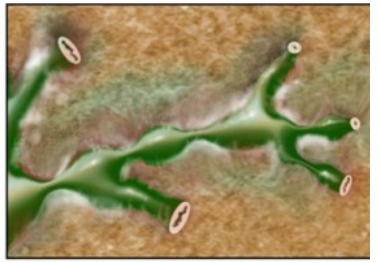
FMT?

Microbiota (Dysbiosis)



Small Duct
PSC

Obliterative fibrosis
of bile ducts



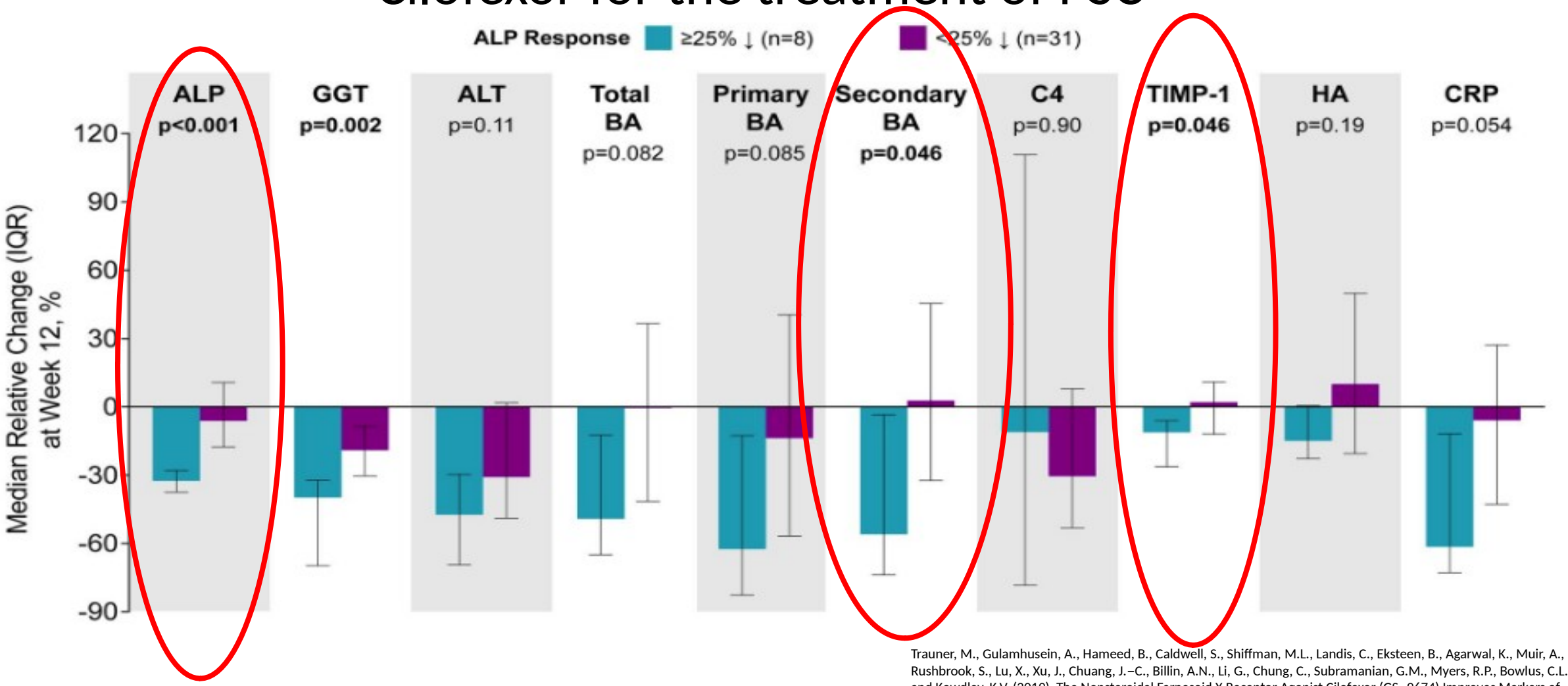
**Large Duct
PSC**

www.mayoclinic.org

Reviews: Hirschfield et al., *Lancet* 2013
Halilbasic et al., *Dig Dis* 2015
Ali et al., *Intract Rare Dis Res* 2015
Karlsen et al., *J Hepatol* 2017

Courtesy Michael Trauner, Vienna

# Cilofexor for the treatment of PSC




Trauner, M., Gulamhusein, A., Hameed, B., Caldwell, S., Shiffman, M.L., Landis, C., Eksteen, B., Agarwal, K., Muir, A., Rushbrook, S., Lu, X., Xu, J., Chuang, J.–C., Billin, A.N., Li, G., Chung, C., Subramanian, G.M., Myers, R.P., Bowlus, C.L. and Kowdley, K.V. (2019), The Nonsteroidal Farnesoid X Receptor Agonist Cilofexor (GS–9674) Improves Markers of Cholestasis and Liver Injury in Patients With Primary Sclerosing Cholangitis. Hepatology, 70: 788-801. doi:10.1002/hep.30509

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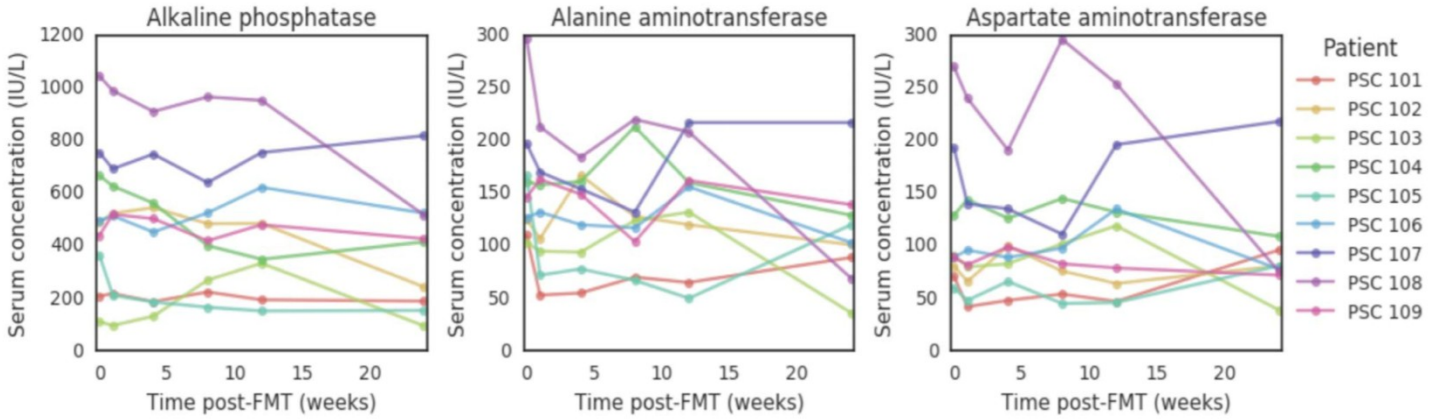
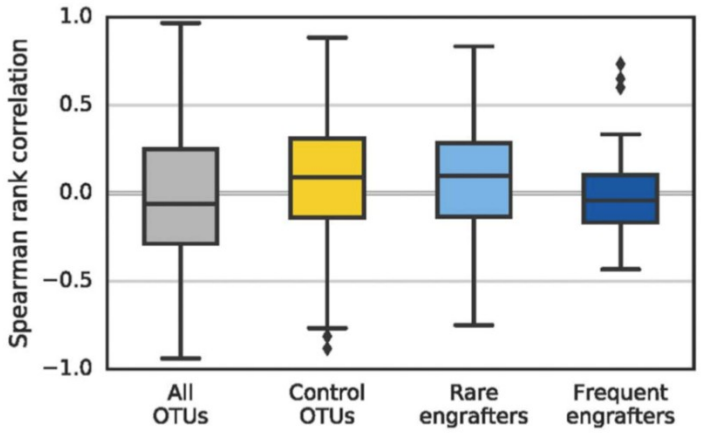
# Fecal Microbiota Transplantation in Patients with PSC

Study Design: An open-label pilot study of 10 patients with PSC with concurrent inflammatory bowel disease and alkaline phosphatase (ALP) > 1.5 x the upper limit of normal. The patients underwent a single FMT by colonoscopy.



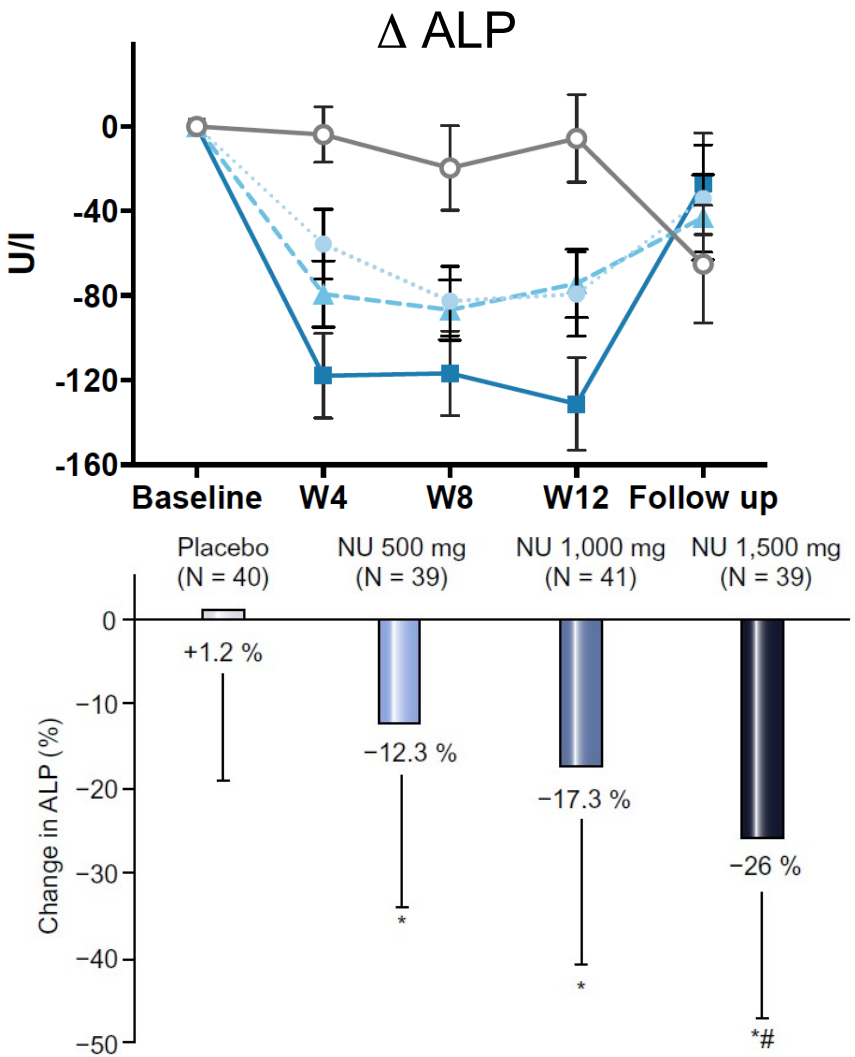



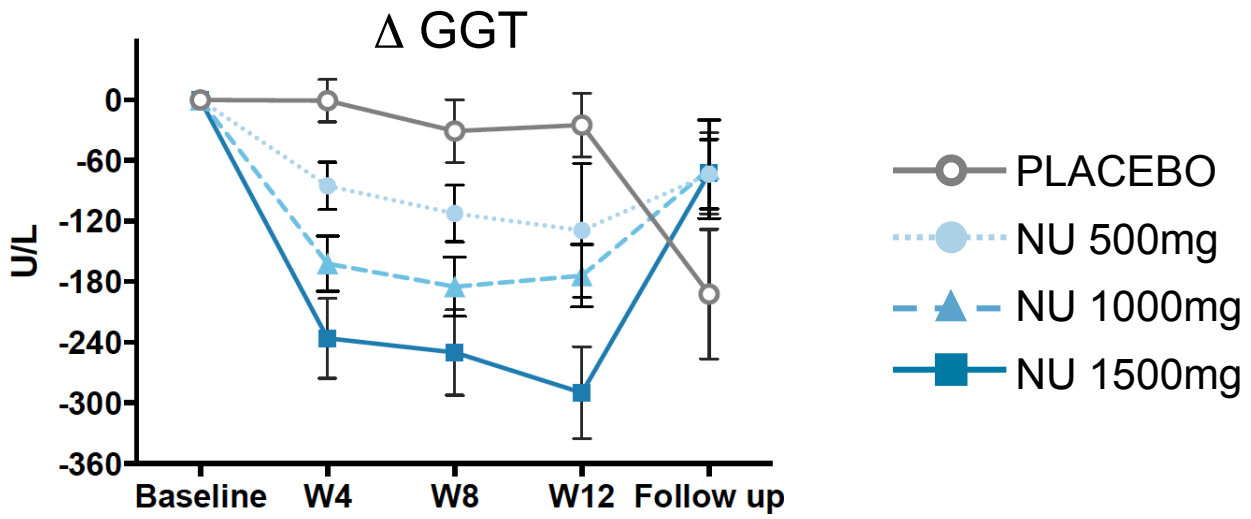

Correlation between change in ALP and change in OTU abundance post-FMT

- ✓ FMT is safe in patients with PSC - there were no related adverse events.
- ✓ Overall, 30% (3/10) experienced a > 50% decrease in ALP levels
- ✓ Abundance of engrafter operational taxonomic units in patients post-FMT correlated with decreased ALP levels

Allegretti JR et al. Am J Gastroenterol 2019

# *nor*UDCA Improves Cholestasis in PSC: Results of a European Multicenter Phase II RCT (NUC-3)




- **Phase III initiated (NUC-5)**

Fickert, …., Manns, Trauner, *J Hepatol* 2017; 67: 549-558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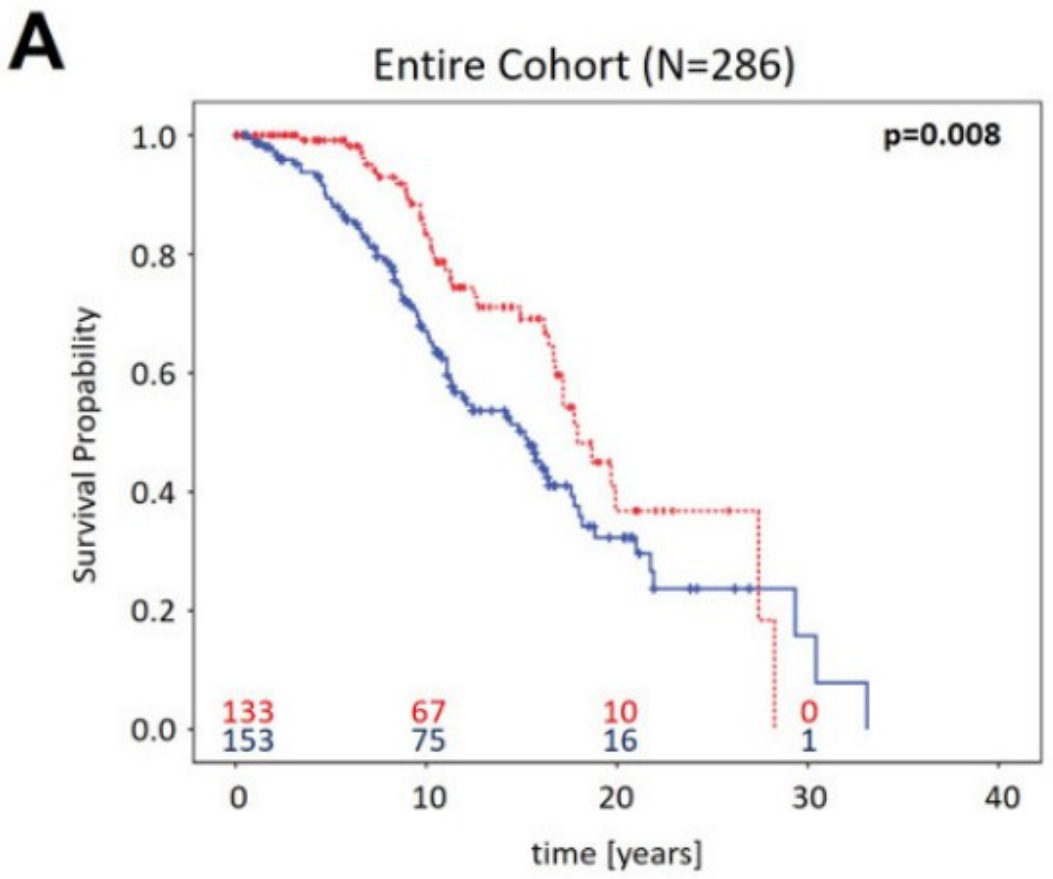
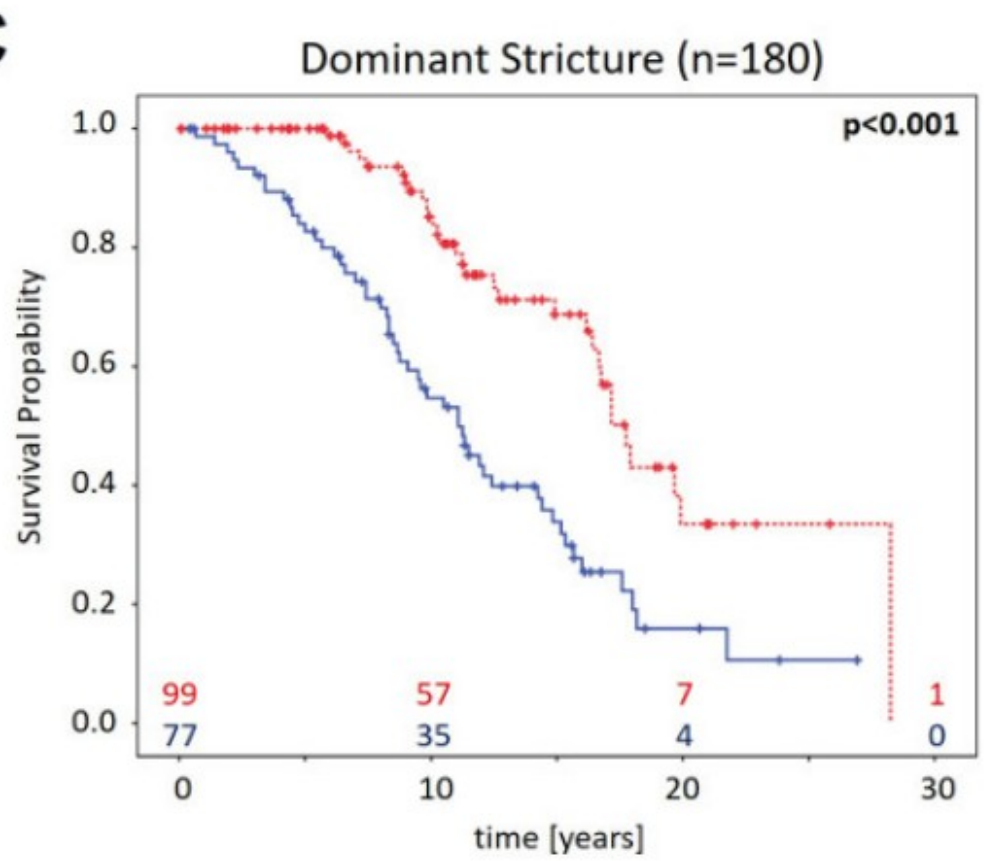
# Scheduled ERCP with dilatation of dominant stenosis improves survival in PSC patients




red = scheduled ERCP; blue = ERCP o-demand

Rupp C, Hippchen T, Bruckner T, et al. Effect of scheduled endoscopic dilatation of dominant strictures on outcome in patients with primary sclerosing cholangitis. *Gut*. 2019. doi:10.1136/gutjnl-2018-316801

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# What is the biggest challenge in PSC ?

**Therapy - Endpoints !**

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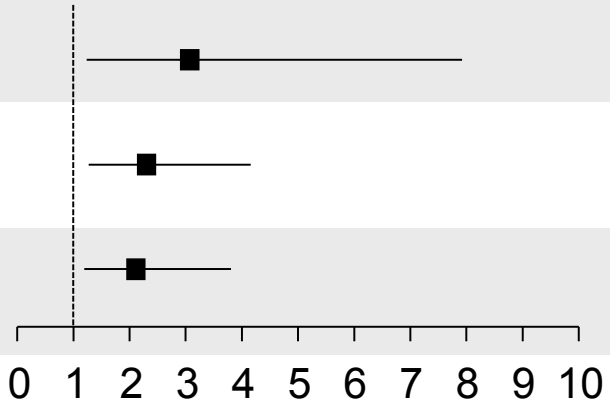
# Results: MRCP Predictors of PSC-Related Clinical Events

Multivariate Analysis




| | HR (95% CI) | p-value | β Coefficient |
|---|---|---|---|
| Hepatic dysmorphy | **3.11** (1.22, 7.92) | **0.018** | **1.13** |
| Portal HTN | **2.31** (1.28, 4.17) | **0.005** | **0.84** |
| Perihepatic nodes ≥10 mm | **2.14** (1.20, 3.81) | **0.010** | **0.76** |

**MRCP Risk Score (MRCP-RS)**

= 1 x Hepatic dysmorphy + 1 x Portal HTN + 1 x Perihepatic nodes

Multivariate Cox regression with backward selection ($p < 0.05$ for variable retention).

Muir, ….Manns, ….. et al, AASLD 2017

# Association between serum IgG levels and clinical course in PSC

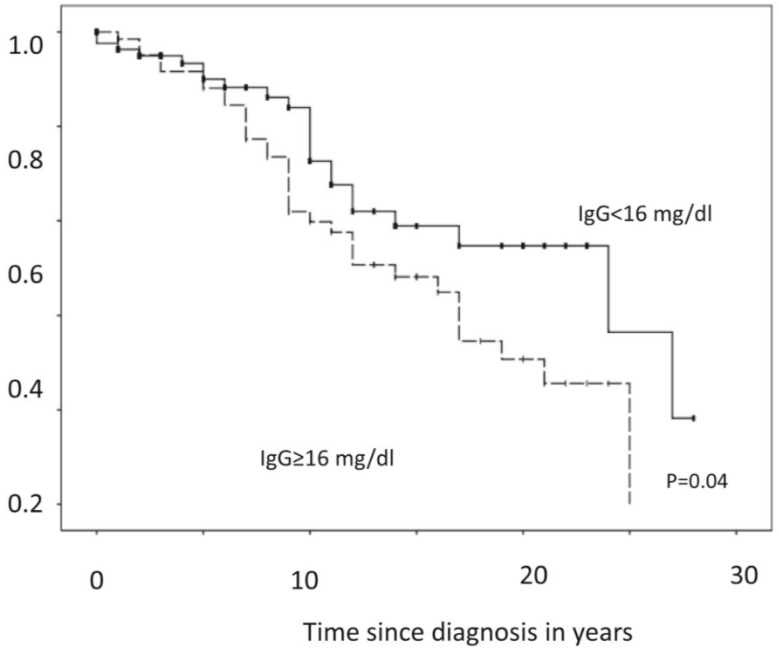



**Table 4** Uni- und multivariate analysis cox regression analyses

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| Risk factors | β-estimate | Exp (B) CL 95% | *p*-value | β-estimate | Exp (B) CL 95% | *p*-value |
| Gender | 0.8 | 0.5–1.4 | 0.5 | 1.3 | 0.5–3.8 | 0.6 |
| Age of diagnose [years] | 1.0 | 0.9–1.0 | 0.07 | 0.9 | 0.9–1.0 | 0.8 |
| Presence of IBD | 1.7 | 0.9–3.4 | 0.1 | 0.8 | 0.3–1.9 | 0.8 |
| Presence of dominant stenosis | 2.6 | 1.4–4.9 | **0.003** | 3.3 | 1.1–9.8 | **0.04** |
| Mayo Risk score | 1.7 | 1.3–2.2 | **0.001** | 1.5 | 1.0–2.1 | **0.03** |
| Immunosuppression | 0.5 | 0.1–2.1 | 0.4 | 0.0 | 0.0–0.0 | 1.0 |
| Biochemical response | 2.0 | 1.2–3.4 | **0.01** | 2.3 | 1.1–5.4 | **0.04** |
| Elevated Serum IgG-levels | 2.4 | 1.1–5.0 | **0.02** | 2.4 | 1.0–5.7 | **0.04** |

Table shows prospective factors for longer survival until death or liver transplantation. In univariate analysis Mayo Risk Score (MRS), presence of dominant stenosis, biochemical response to UDCA and elevated serum IgG levels were associated with reduced survival. In multivariate analysis, MRS, presence of dominant stenosis, biochemical response to UDCA and elevated serum IgG-levels were independently associated with reduced transplantation-free survival ($p < 0.05$). Bold values indicates significant *P*-values (<0.05)

- ✓ Elevated serum IgG levels at first diagnosis count as an independent risk factor for reduced transplant free-survival in patients with PSC
- ✓ Serum igG levels might be taken into account for planning individual, risk-adapted screening and surveillance strategies
- ✓ Further validation is needed

Hippchen T et al. BMC Gastroenterology 2019

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# Autoimmune hepatitis

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13.01.2020

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# What´s new about the pathophysiology of AIH with relevance to treatment ?

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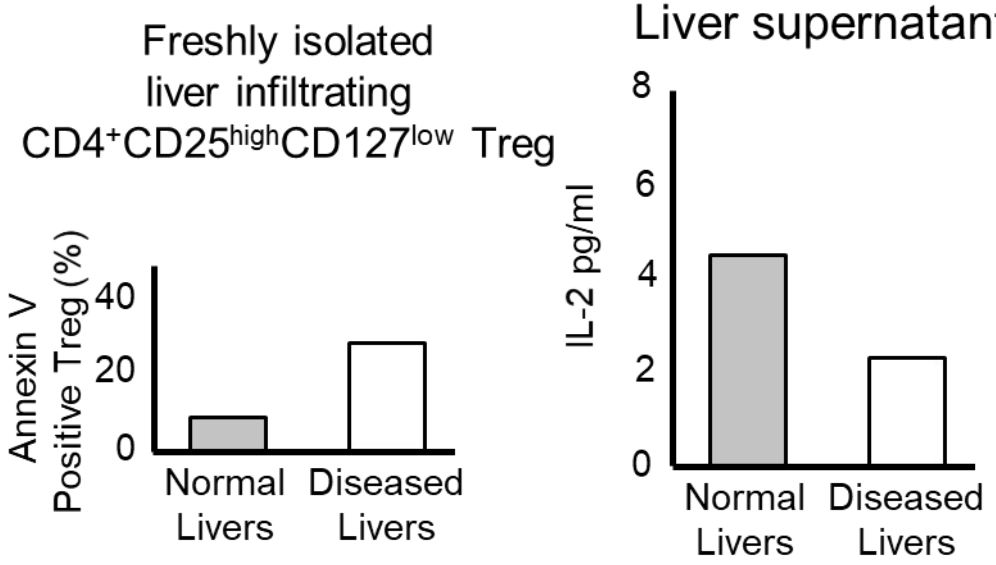
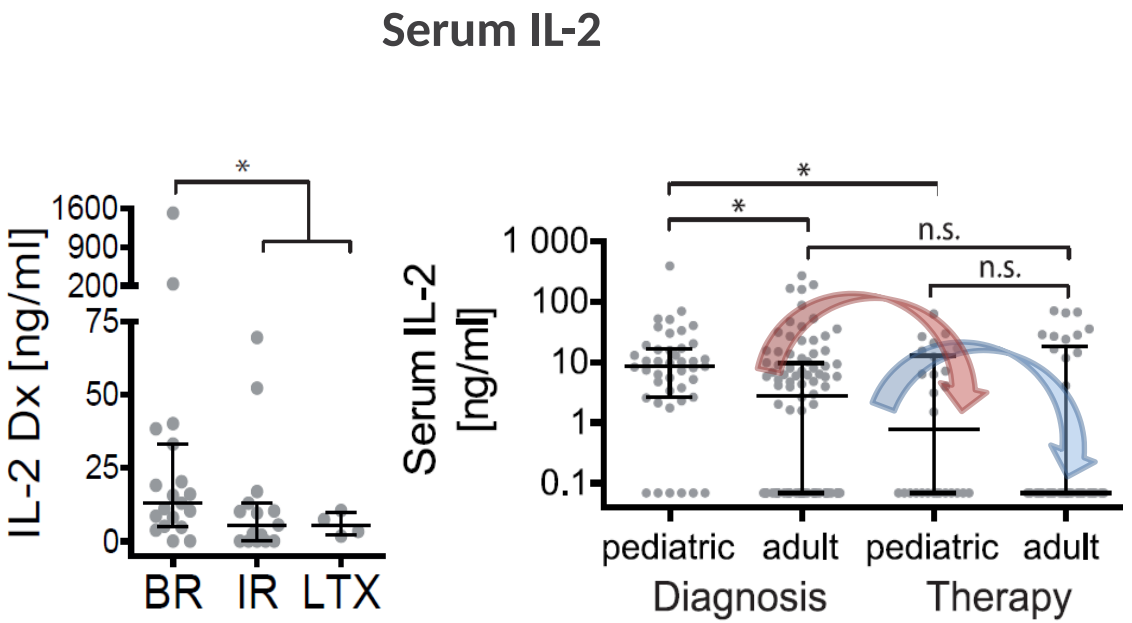
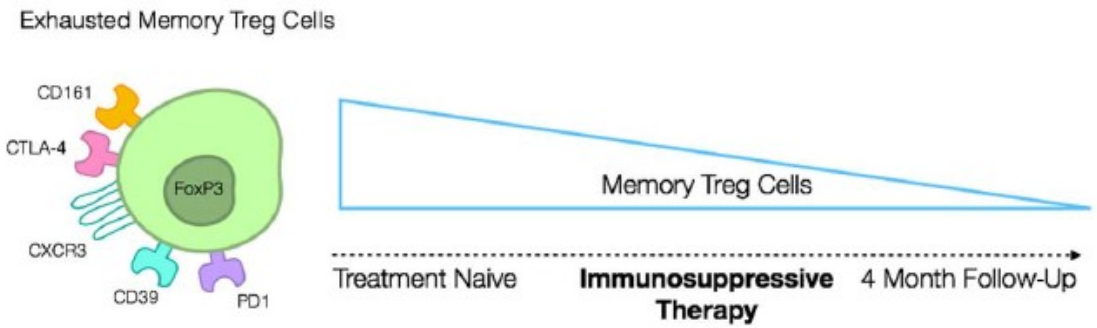
# Regulatory T cells (Treg): Numbers and function




Chen et al. Hepatology. 2016 Jul;64(1):138-50




Diestelhorst et al. PLoS One. 2017;12(7):e0181107
Diestelhorst et al. Sci Rep. 2018 Jan 11;8(1):419.




modified from: Jeffery et al. HEPATOLOGY COMMUNICATIONS, Vol. 2, No. 4, 2018

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# What´s new about diagnosing AIH ?

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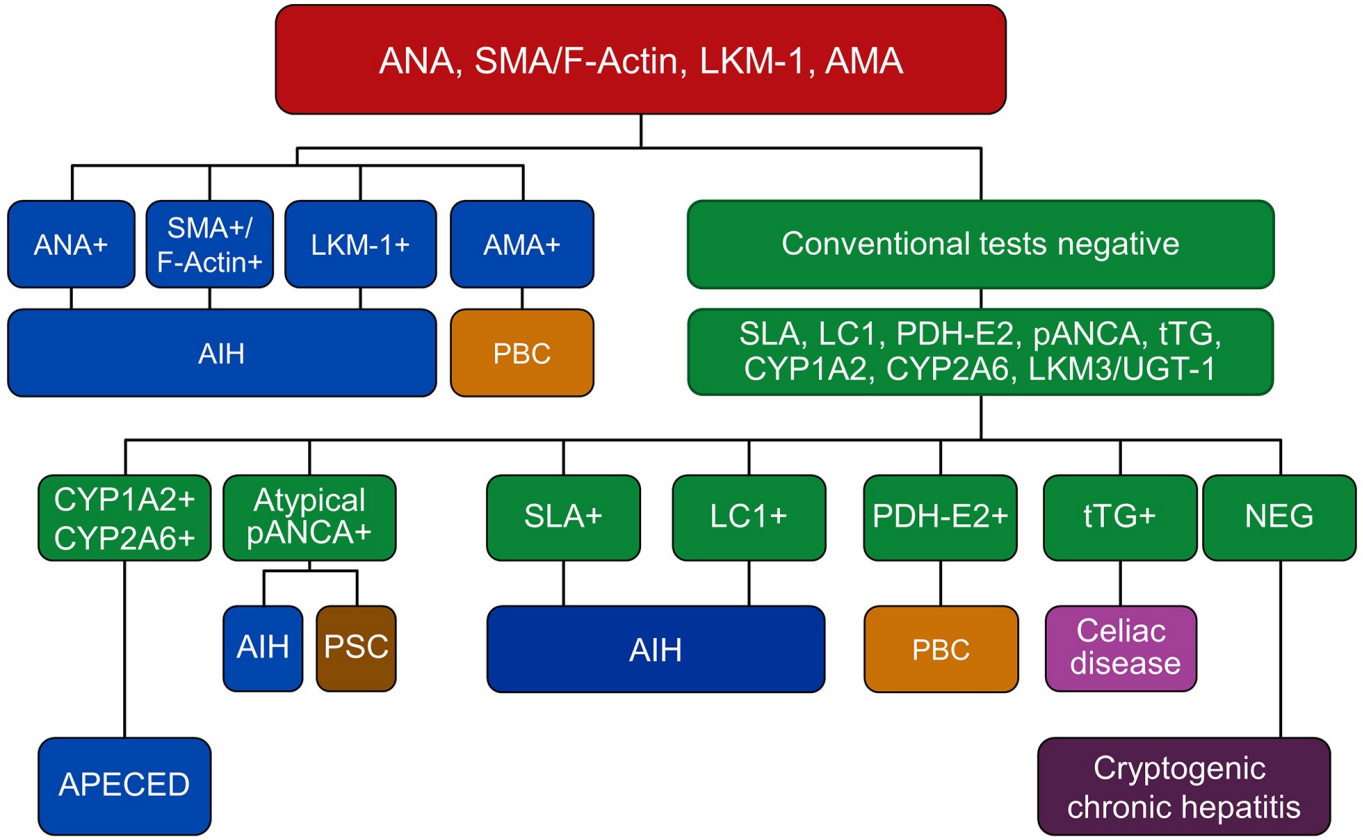
# Diagnostic Autoantibody Algorhythm for the Diagnosis of Autoimmune Liver Disease




**Mack……., Manns,….et al AASLD AIH CPG, in press 2020**

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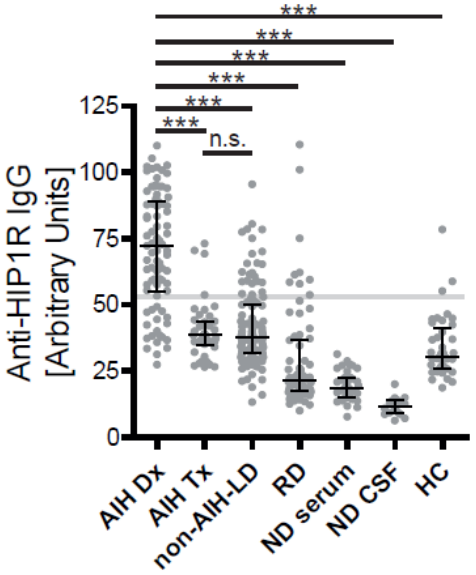
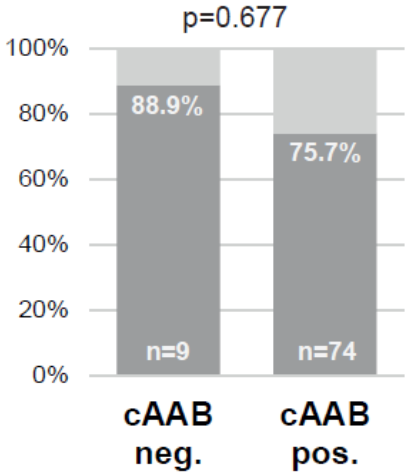
# Anti-HIP1R* for the diagnosis AIH

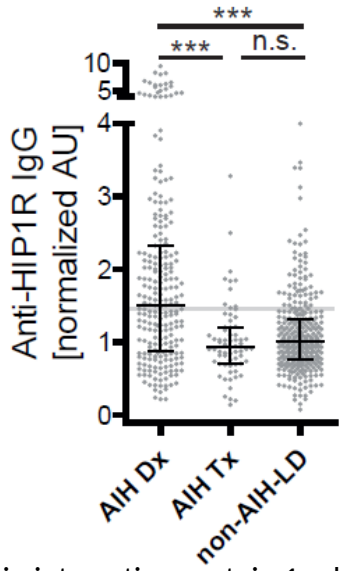

Hannover Training Cohort (n=207)



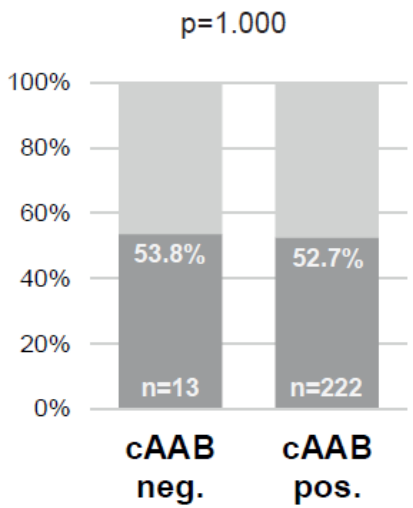

| | Anti-HIP1R positivity |
|---|---|
| AIH Dx | 77.1 % |
| AIH Tx | 9.5 % |
| non-AIH-LD | 19.4 % |
| RD | 12.7 % |
| ND serum | 0.0 % |
| ND CSF | 0.0 % |
| HC | 7.3 % |




European Validation Cohort (n=558)




| | Anti-HIP1R positivity |
|---|---|
| AIH Dx | 56.2 % |
| AIH Tx | 16.4 % |
| non-AIH-LD | 22.3 % |




anti-HIP1R pos.
anti-HIP1R neg.

AIH Dx = untreated AIH
AIH Tx = AIH unter treatment
non-AIH-LD = non-AIH-liver disease
RD = rheumatological disease
ND = neurological disease
HC = healthy control
cAAB= conventional autoantibodies

Equal sensitivity in autoantibody negative AIH

Taubert, Engel, … Manns, Jaeckel submitted

*Huntingtin interacting protein 1 related protein - ubiquites protein

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# Anti-HIP1R for the diagnosis AIH

| | | Sample number | Sensitivity | p vs HIP1R | Specificity | p vs HIP1R | Accuracy | CI |
|---|---|---|---|---|---|---|---|---|
| Retrospective training cohort (Hannover) | **anti-HIP1R** | **207** | **0.771** | | **0.806** | | **0.792** | **0.729-0.844** |
| | **ANA** | 207 | 0.819 | 0.572 | 0.677 | 0.033 | 0.734 | 0.668-0.792 |
| | **SMA** | 207 | 0.427 | <0.001 | 0.637 | 0.002 | 0.553 | 0.483-0.622 |
| | **anti-LKM** | 205 | 0.037 | <0.001 | 1.000 | not applicable | 0.620 | 0.549-0.686 |
| European multicenter validation cohort | **anti-HIP1R** | **558** | **0.528** | | **0.802** | | **0.686** | **0.646-0.724** |
| | **ANA** | 558 | 0.711 | <0.001 | 0.591 | <0.001 | 0.642 | 0.600-0.681 |
| | **SMA** | 558 | 0.672 | 0.002 | 0.728 | 0.020 | 0.704 | 0.664-0.742 |
| | **anti-LKM** | 395 | 0.027 | <0.001 | 0.994 | <.0001 | 0.448 | 0.399-0.499 |

Anti-HIP1R more specific than ANA and SMA

Taubert, Engel, … Manns, Jaeckel submitted

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# What´s new about therapies for AIH?

## Induction therapy

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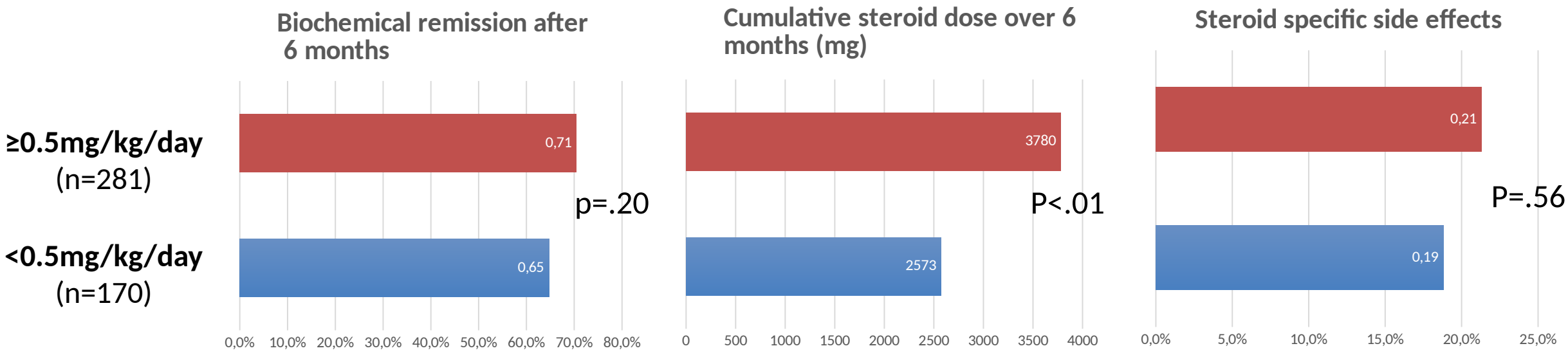
# Differences of high (≥0.5mg/kg) and low (<0.5mg/kg) dose prediso(lo)ne regimen during first line therapy

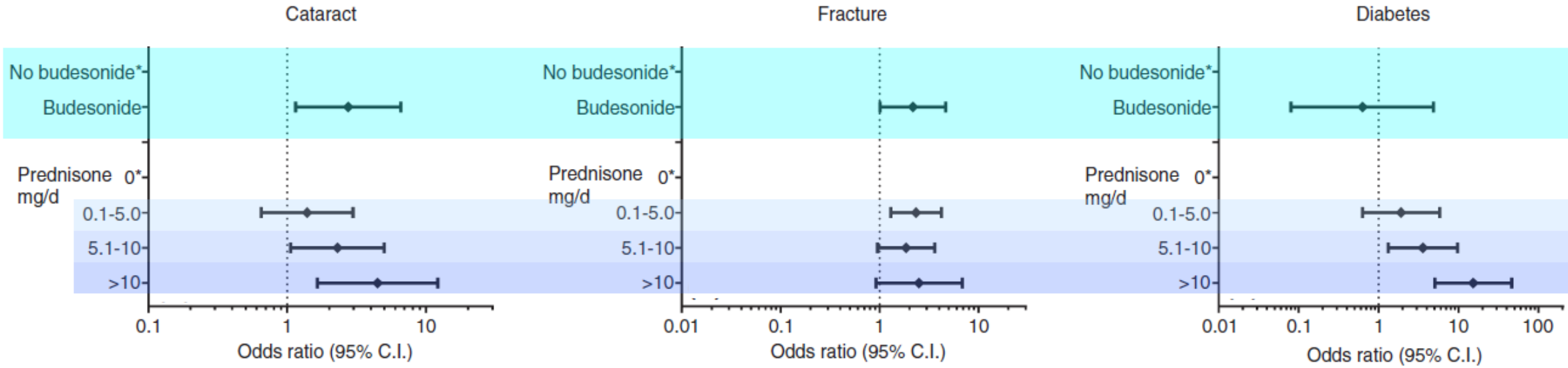
451 AIH patients from 9 centers in 5 European countries treated between 1978 and 2017




Pape et al. Clin Gastroenterol Hepatol. 2019 Jan 5.

# Adverse events related to low dose corticosteroids in autoimmune hepatitis

476 AIH patients with a total of 6634 patient years
from Dutch AIH Study Group Registry since 2008




Van den Brand et al. Aliment Pharmacol Ther. 2019 Oct 15. doi: 10.1111/apt.15528

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# What´s new about therapies for AIH ?

## Salvage therapy

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# First Meta-Analyses for AIH 2017-2019

| Study | | Study cohort | Patients | Drugs | Treatment response | Adverse events (AE) | Conclusion |
|---|---|---|---|---|---|---|---|
| Yu et al. 2019 | Meta-Analysis of 7 studies | MMF as first line therapy | 583 | MMF+prednisone<br>Standard of care (SOC) | ALT/AST normalization: 55-89% vs 33-87% (p < 0.05)<br>IgG normalization: 62-89% (p < 0.01)<br>non-response 6-33% (p < 0.01)<br>AST/ALT/IgG normalization: 33-87%<br>non-response 15-67% (p < 0.01) | | MMF+Pred superior to SOC |
| De Lemos-Bonotto et al. 2018 | Meta-Analysis of 15 studies | Second line therapy agents | 283 | MMF+prednisone<br>Tacrolimus+prednisone | improvement of aminotransferases 79%<br>histological remission 89%<br>improvement of aminotransferases 94% | liver transplantation 11%<br>mortality 7 % | Tac+Pred best for improvement of aminotranferases |
| Santiago et al. 2019 | Meta-Analysis of 12 studies | | | | | %<br>uation<br>ffects 8% | switch to MMF was effective (better for intolerance than for non response) |
| Zizzo et al. 2017 | Meta-Analysis of 15 studies | Second line therapy agents in children | 76 | MMF<br>Ciclosporin<br>Tacrolimus | normalization of ALT/AST at 6 months: 36%<br>normalization of ALT/AST at 6 months: 83%<br>normalization of ALT/AST at 6 months: 50% | pooled estimates for AE: 45%<br>pooled estimates for AE: 78%<br>pooled estimates for AE: 42% | CsA most effective but most AEs |

**None of the second line therapies for AIH treatment failure are approved yet !**


Yu et al. Eur J Gastroenterol Hepatol. 2019 Jul;31(7):873-877.
De Lemos-Bonotto et al. Eur J Gastroenterol Hepatol. 2018 Feb;30(2):212-216.
Santiago et al. Aliment Pharmacol Ther. 2019 Apr;49(7):830-839.
Zizzo et al. J Pediatr Gastroenterol Nutr. 2017 Jul;65(1):6-15.

# Management of Treatment Failures after Standard of Care: SOC

- Biologics
  - Anti TNF
  - Anti CD 20 (Rituximab)
  - Anti B cell and anti BAFF-R (VAY736)

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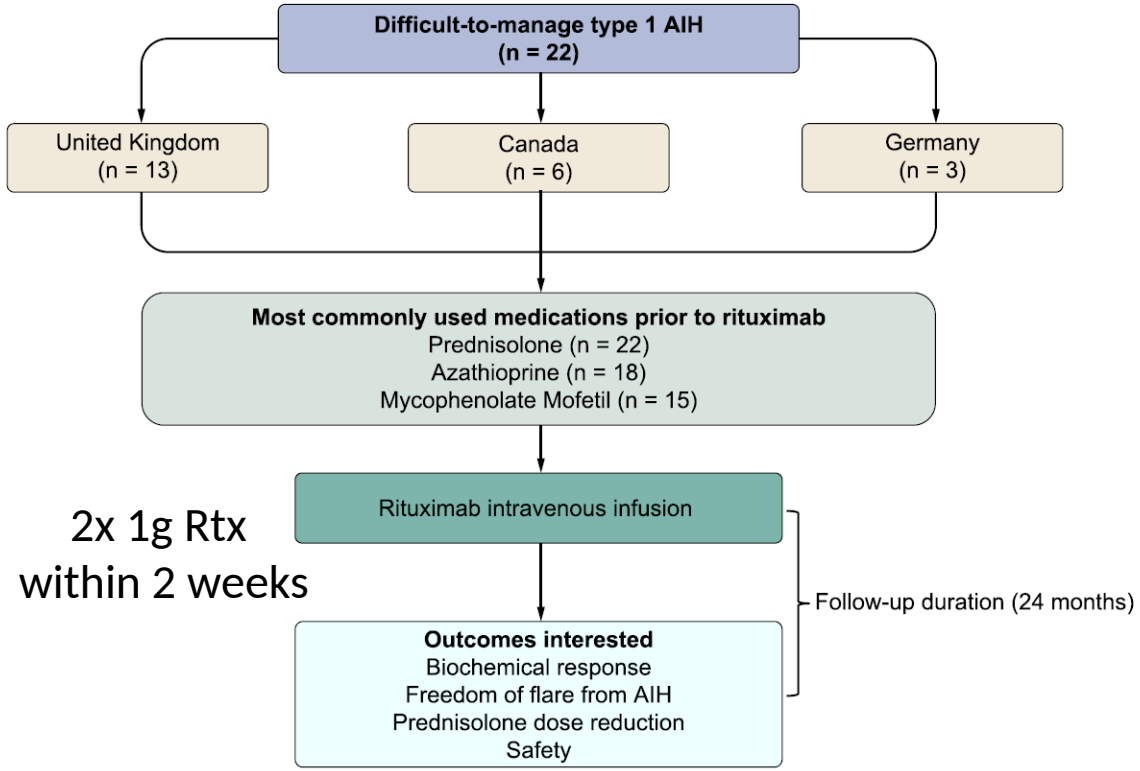
# Rituximab for difficult to manage AIH

retrospective **IAIH group study**

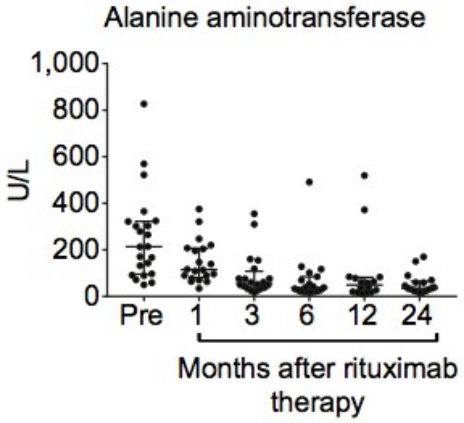
*incl. 3x Cirrhosis (2x CP A; 1x CP C)*

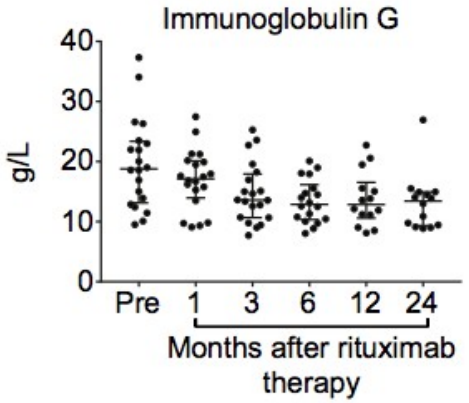


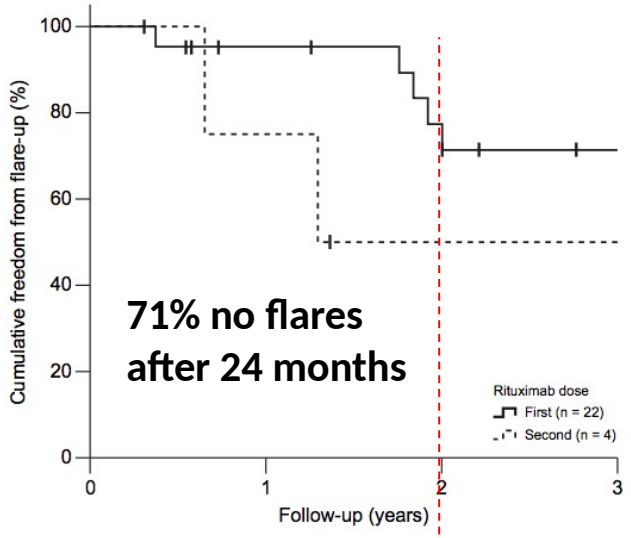

2x 1g Rtx
within 2 weeks

**No serious adverse event**

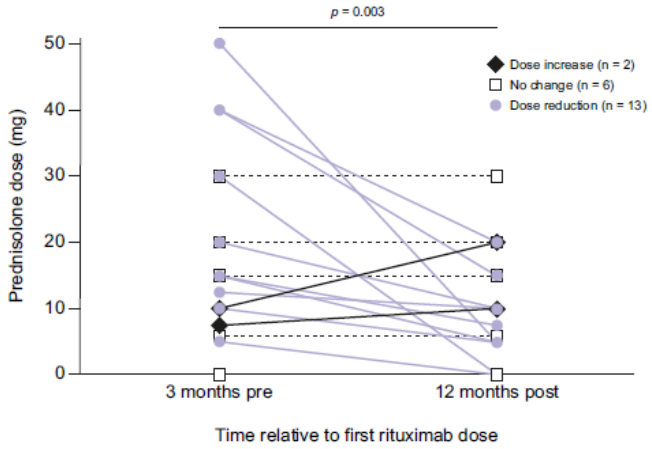
**Modified from Than NN, …. Taubert R … Manns MP, … et al.**
**JHEP Reports, Volume 1, Issue 6, 437 – 445, 2019**



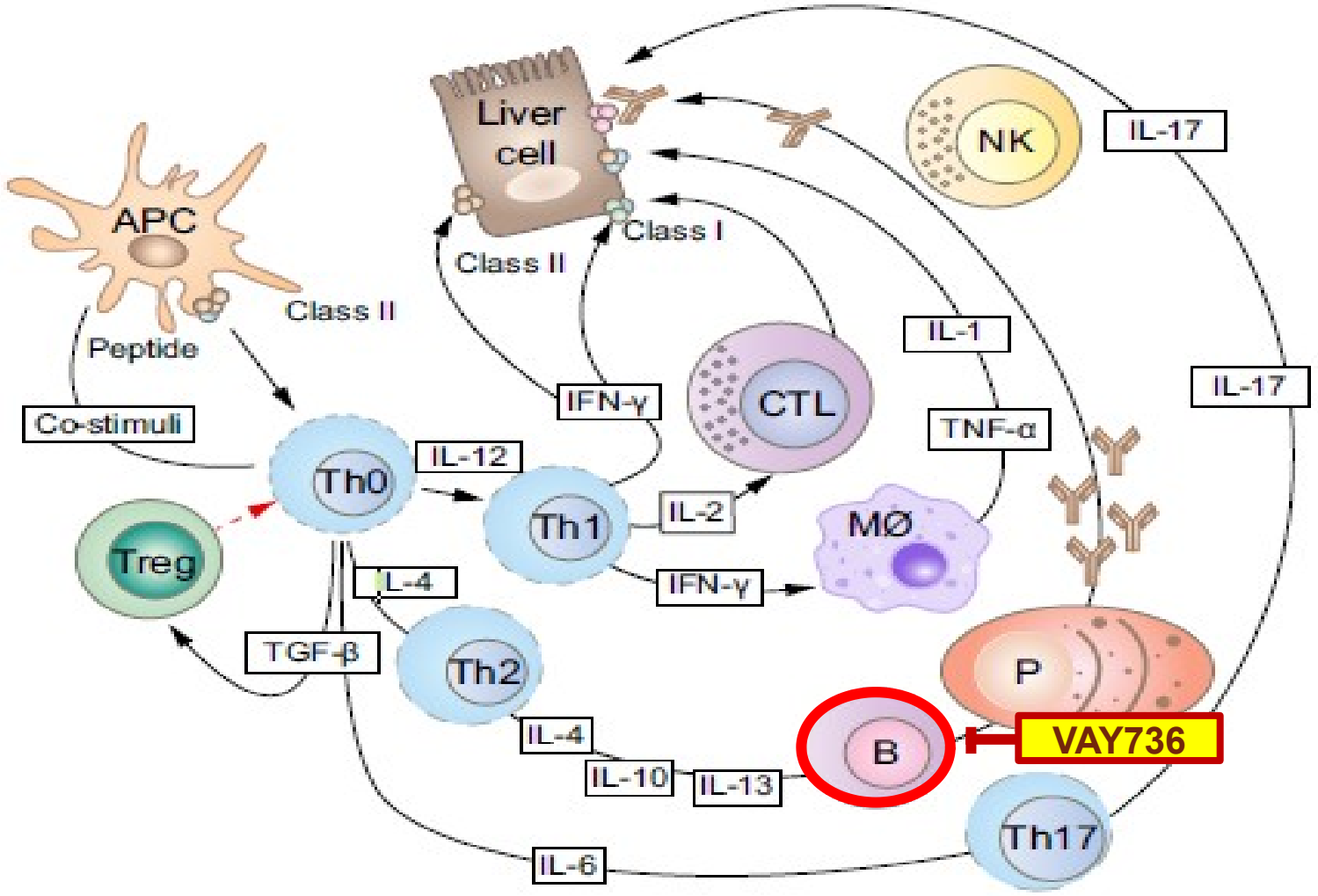




**62% Steroid dose reduction**



# Molecular Pathogenesis of autoimmune hepatitis




**Manns et al., Journal of Hepatology, 2015**





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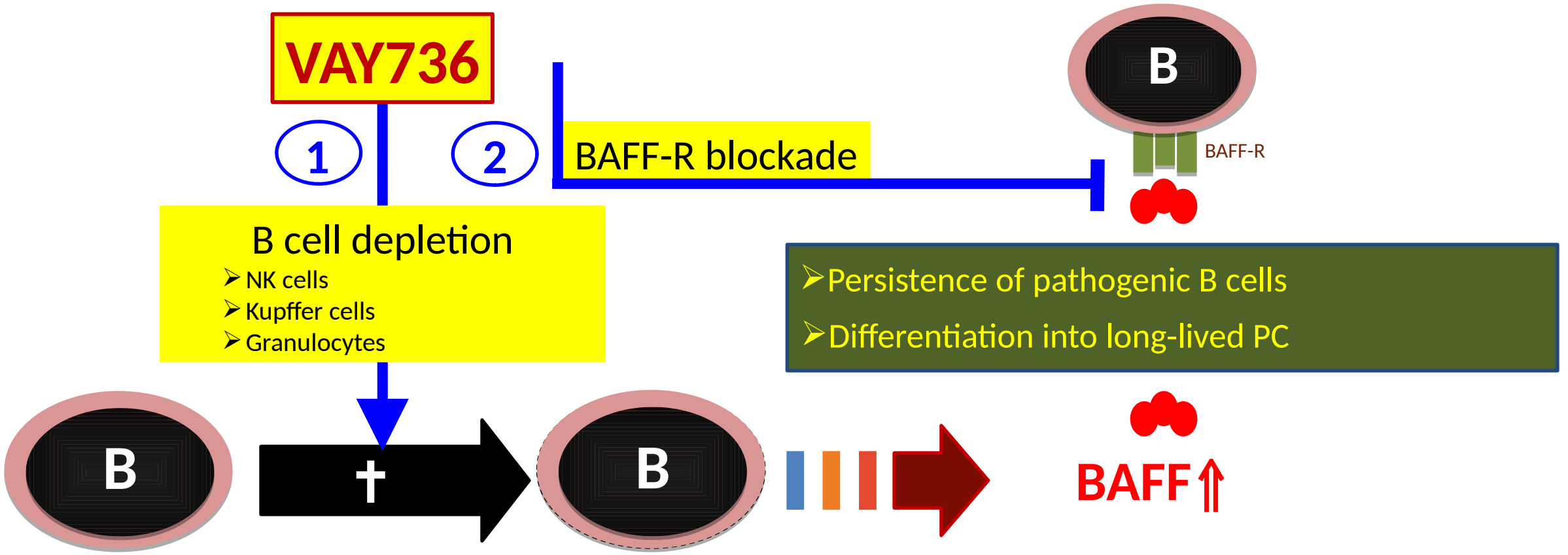
# VAY736: Anti-BAFF-R antibody with dual action

1) ADCC mediated B cell depletion; 2) Functional BAFF-R blockade




**Rapid and profound B cell depletion | Prevention of BAFF-induced hardening of autoimmunity**

www.clinicaltrials.gov: NCT03217422

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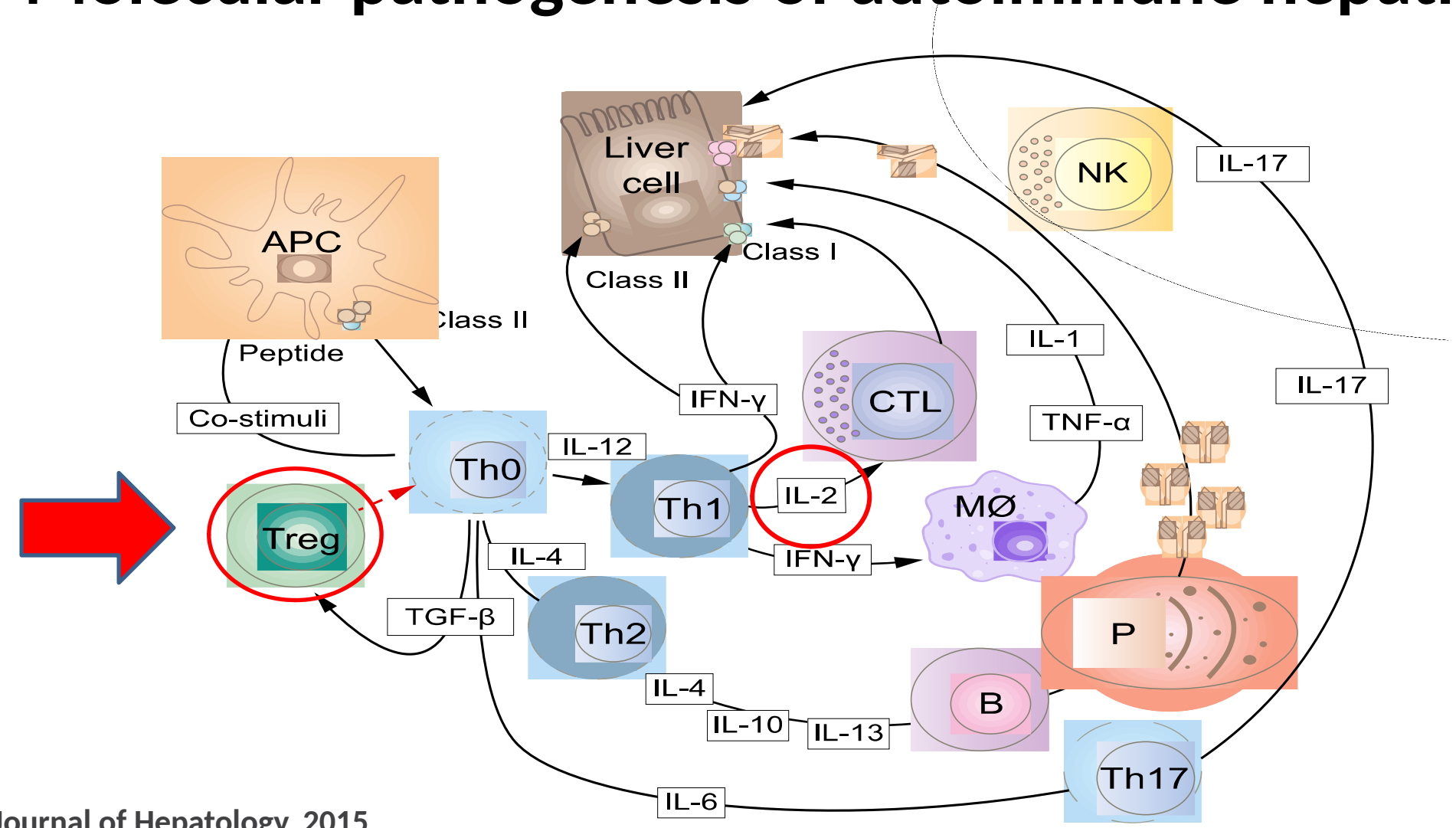
# Molecular pathogenesis of autoimmune hepatitis




Manns et al., Journal of Hepatology, 2015

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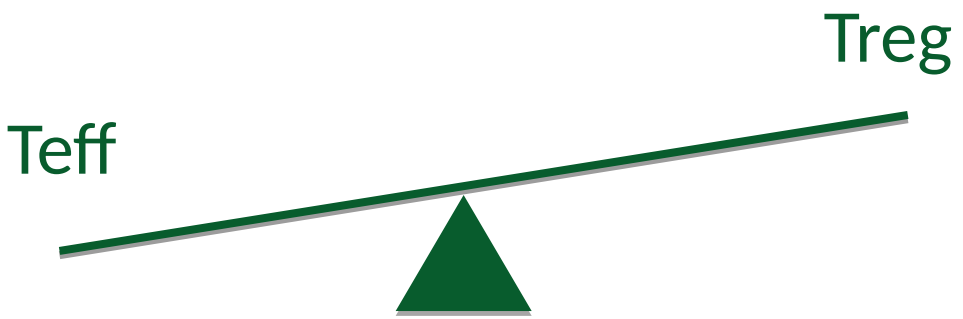
# AIH: Future Therapies

- Can we increase therapeutic response by strengthening immunoregulation ?
- Adoptive transfer of Tregs ?
- Low dose IL-2 ?

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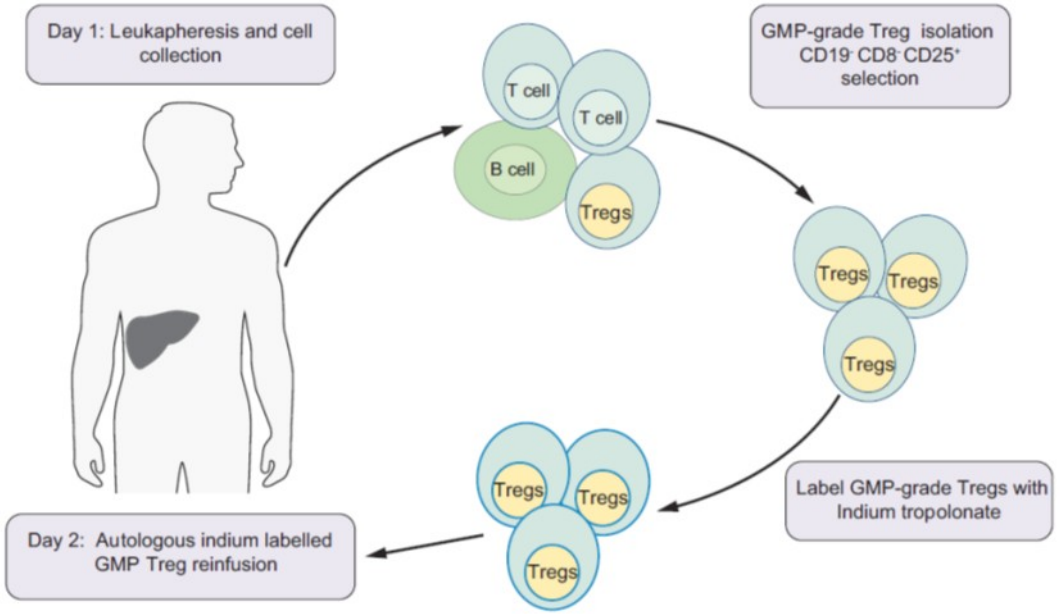
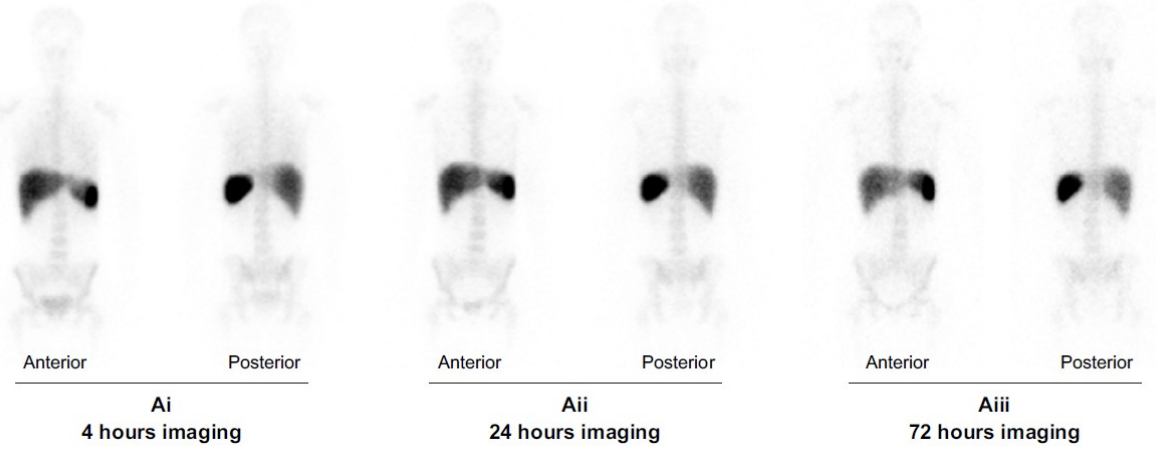
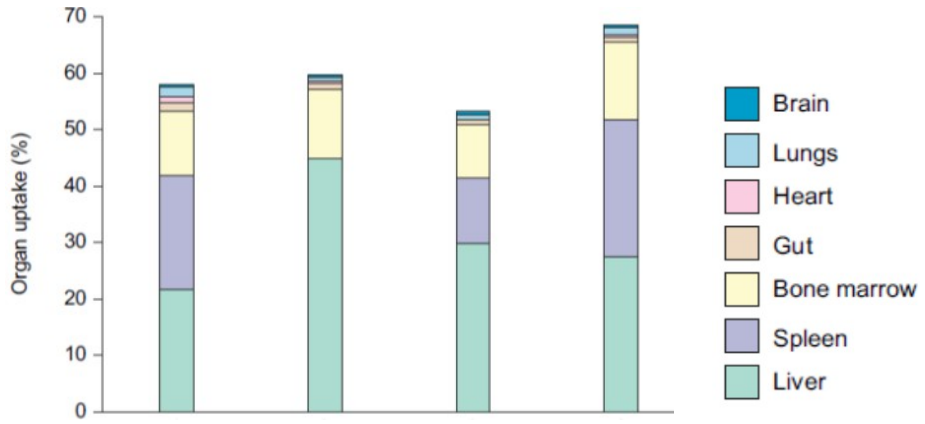
# Clinical Treg infusion in AIH patients – a pilot trial




- Inclusion 5 pts; Treg infusion in 4 pats. (labelling failure)
- Isolated Treg were functional
- 22-44% of Treg homed and were retained in the liver
- No off target accumulation beside spleen and bone marrow
- No infusion reaction or serious adverse event

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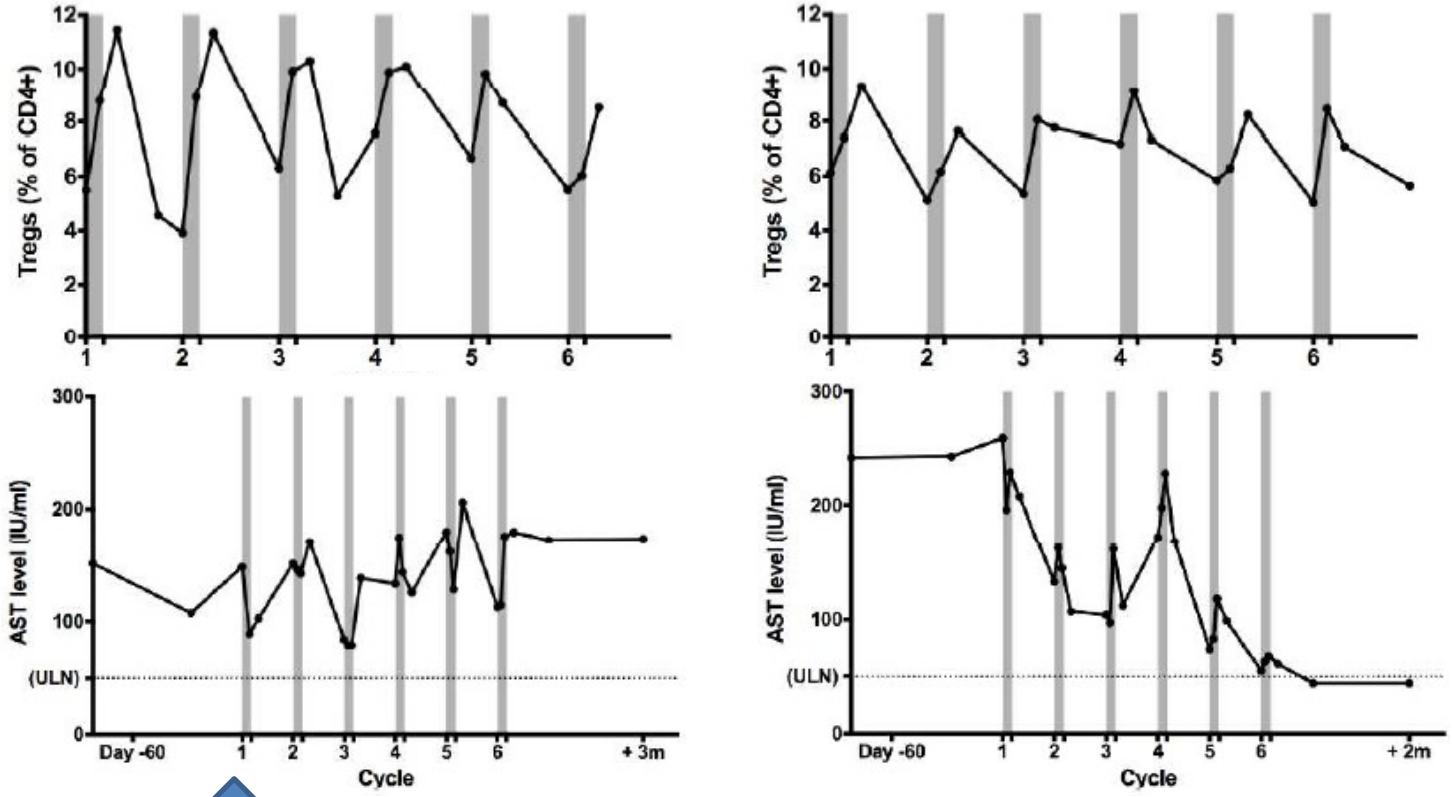
**Modified from Oo et al. JHEP Reports 2019. Vol. 1, Issue 4, Pages 286-296**

# Low dose IL-2 in refractory AIH

female 20 yrs. with cirrhosis
(pediatric AIH-1)

female 56 yrs. with bridging fibrosis
(adult AIH-3)




IL-2 ⬆ (1 Mio. Units s.c. 5x/month over 6 months)

Modified from Lim et al., Hepatology. 2018 Oct;68(4):1649-1652

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# What´s new about initiatives for AIH as orphan disease ?

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# European Reference Network

for rare or low prev
complex diseases

**Network**
Hepatological Disea
(ERN RARE-LIVER)

Lead:
Prof. Lohse
Hamburg/Germany

**Full Members**

| | |
|---|---|
| BE | University Hospitals Saint-Luc<br>University Hospital Leuven<br>University Hospital Ghent |
| DK | Copenhagen University Hospital Rigshospitalet |
| FR | Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre<br>Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Antoine<br>Assistance Publique-Hôpitaux de Paris, Hôpital Beaujon |
| DE | Medizinische Hochschule Hannover<br>Universitätsklinikum des Saarlandes<br>Universitätsklinikum Tübingen<br>Uniklinik RWTH Aachen<br>Universitätsklinikum Hamburg-Eppendorf |
| IT | S. Gerardo Hospital - Monza<br>Hospital San Paolo - Milan<br>AO Padua |
| NL | Academic Medical Center Amsterdam<br>University Medical Center Groningen<br>Radboud University Medical Center Nijmegen |
| PL | University Hospital, Banacha, Warsaw |
| PT | Centro Hospitalar e Universitário de Coimbra, EPE |
| ES | Hospital Clínic i Provincial de Barcelona<br>Hospital Universitario La Paz |
| SE | Karolinska University Hospital<br>Sahlgrenska University Hospital |
| UK | The Newcastle upon Tyne Hospitals NHS Foundation Trust<br>Royal Free London NHS Foundation Trust<br>University Hospitals Birmingham NHS Foundation Trust<br>Birmingham Children's Hospital NHS Foundation Trust |

Brexit ???

The network aims to improve the standards of care and clinical knowledge in rare liver diseases across Europe.

**+ ERN registry (prospective registry)**
**+ CPMS (EU Clinical patient management systems)**

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# International AIH Group Initiatives

www.iaihg.org

**Retrospective Registry** in addition to prospective ERN Rare Liver registry

Creating „critical mass“ for research in orphan diseases

Contact: Ynto de Boer (y.deboer1@amsterdamumc.nl) and
Rodrigo Liberal (rodrigo.liberal@kcl.ac.uk)

# Take Home Messages: The Future of Autoimmune Liver Diseases

- New biomarkers are needed to predict non-response to UDCA in PBC
- Obeticholic acid (OCA) and bezafibrate are used for non-response to UDCA in PBC, the combination of both and novel drugs like Selective peroxisome proliferator-activated receptor (PPAR) and fibroblast growth factor 19 (FGF19) agonists are under development.
- There is no existing treatment that alters the natural course of PSC apart from transplantation
- Several medical therapies for PSC are under clinical development like Nor-UDCA, Fecal Microbiota Transplantation (FMT) and others.
- However, generally accepted treatment endpoints as well as biomarkers for the risk-stratification are still needed for the development of novel PSC therapies
- Therapies for non-responders to standard-of-care are an unmet need for AIH patients
- Promising AIH therapies under development are targeting B cells, cytokines like TNF, IL 2 and Tregs

**Michael Manns** **PHC 2020, Paris, 13 Januar 202**

# THANK YOU FOR YOUR ATTENTION

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