Autoimmune and cholestatic liver diseases

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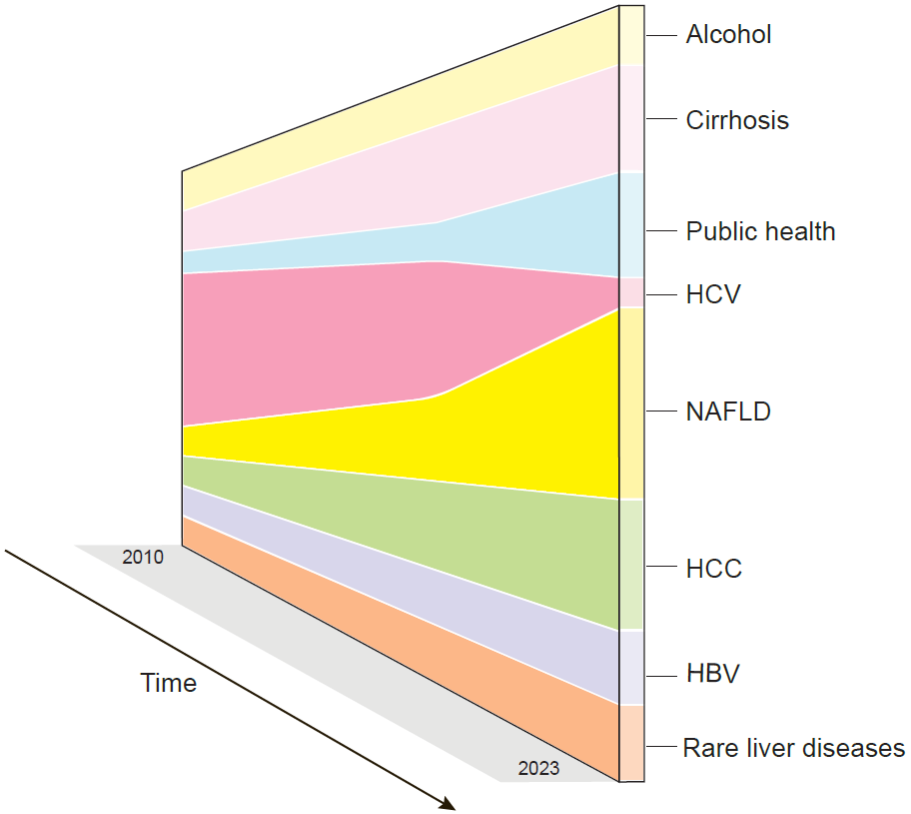
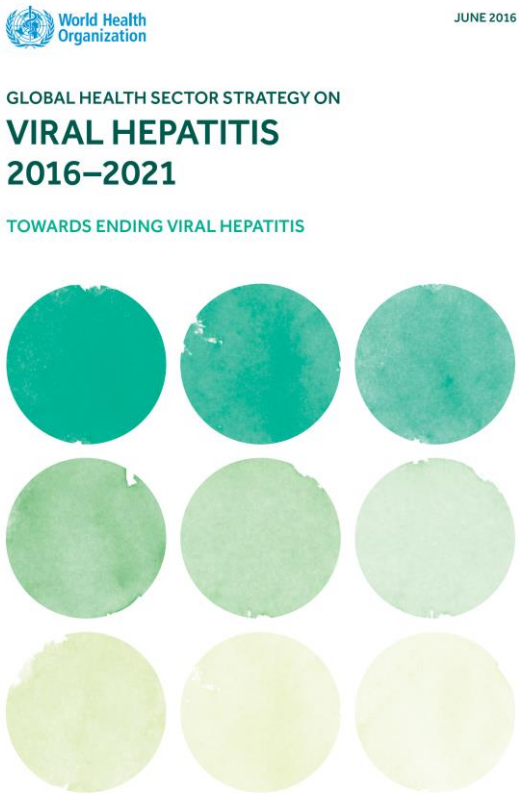
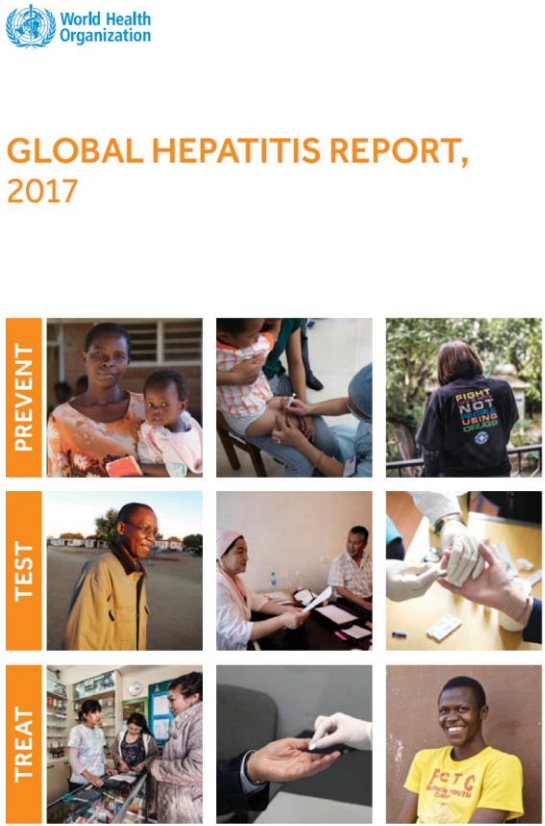
A changing landscape of liver research



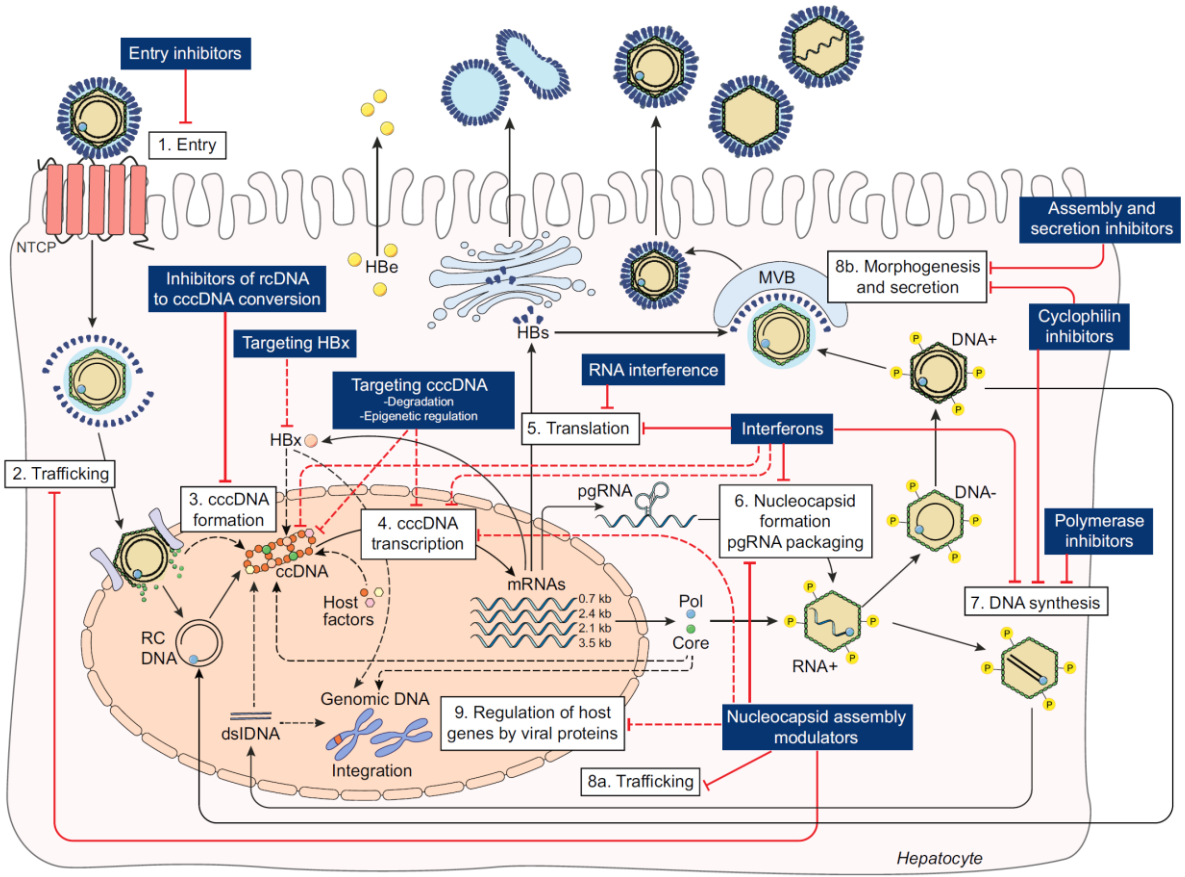
(Karlsen and Tacke, 2018)

Viral hepatitis elimination and public health



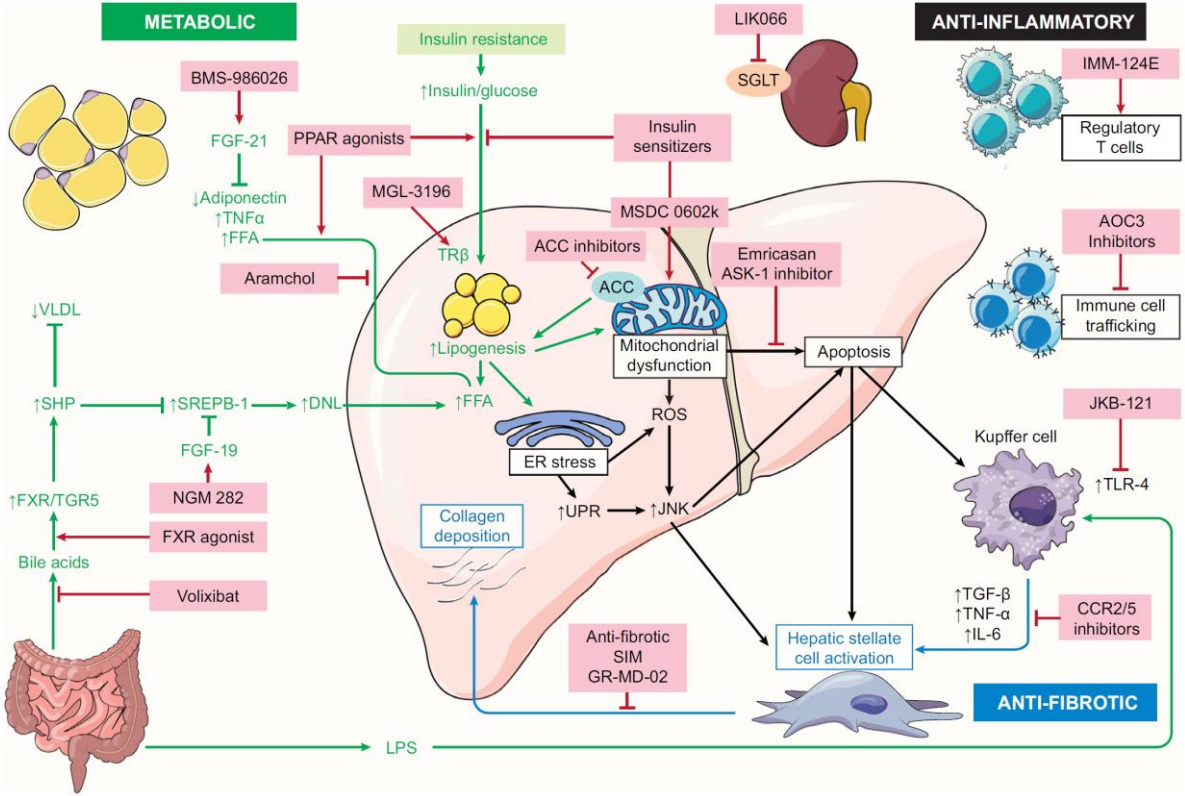


How to accomplish HBV cure?



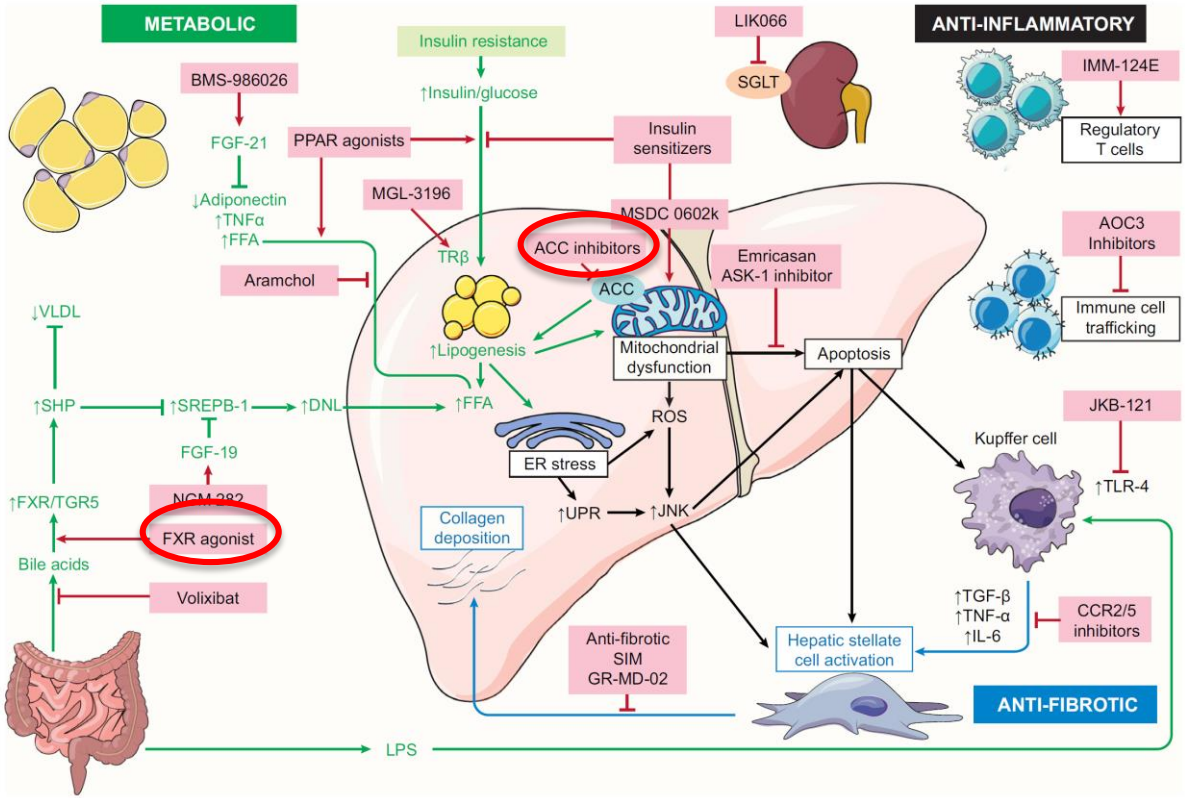
(Lok et al., 2017)

The race for new NAFLD drugs to market



(Konermann et al., 2017)

The race for new NAFLD drugs to market



(Konermann et al., 2017)

Liver oncology and new drugs in HCC

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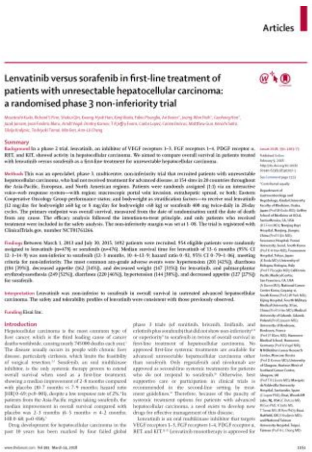
Articles

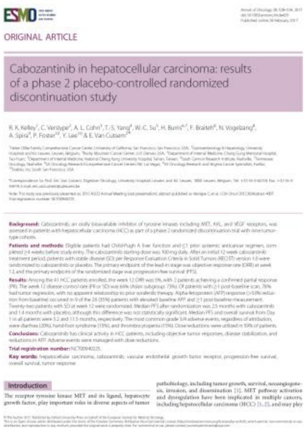
Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial


Articles

Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial

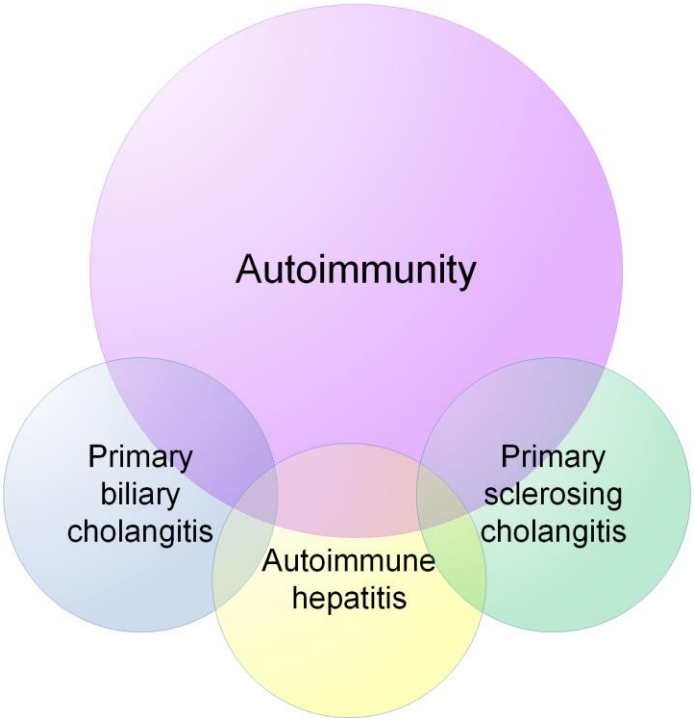

Articles

Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial

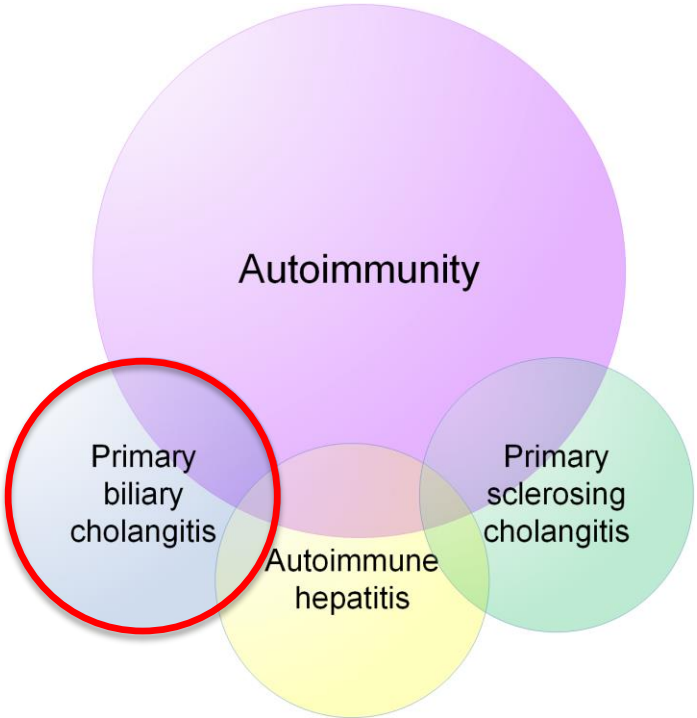

ORIGINAL ARTICLE

Cabozantinib in hepatocellular carcinoma: results of a phase 2 placebo-controlled randomized discontinuation study

So what about autoimmune and cholestatic?



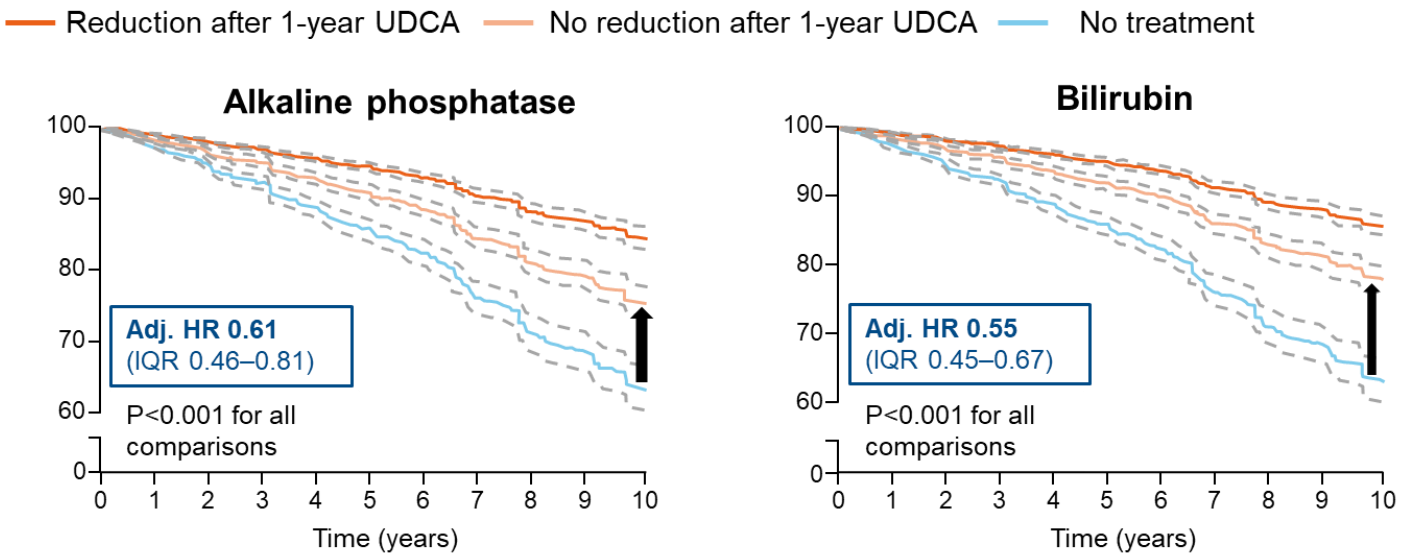
Primary biliary cholangitis



Ursodeoxycholic acid in PBC

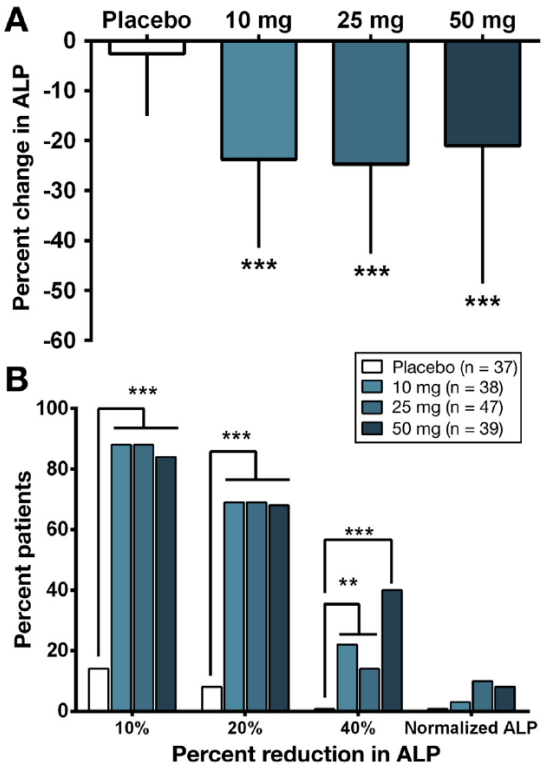
- Barcelona (ALP 40% decrease or normalization) – 39%
- Paris (ALP<3ULN, AST<2ULN, bilirubin<1mg/dl) – 39%
- Rotterdam (bilirubin and albumin normalization) – 24%
- Toronto (ALP <1.67ULN and/or bilirubin <1mg/dl) – 43%
- Mayo (ALP<2ULN or bilirubin 1mg/dl) – 52%
- New algorithms occurring regularly

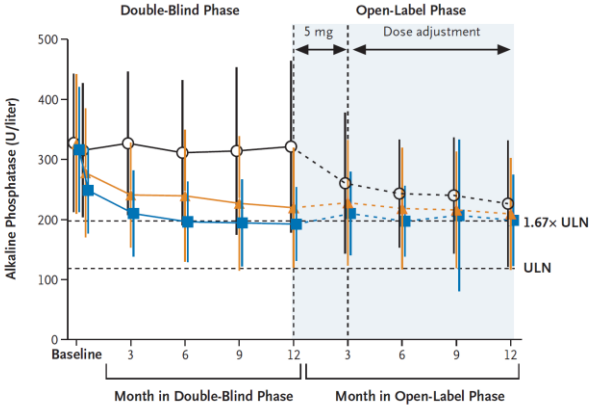
UDCA without biochemical improvement?

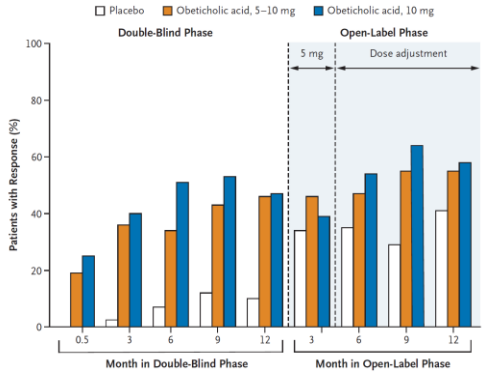


Harms et al., EASL 2018

OCA – phase II and phase III studies

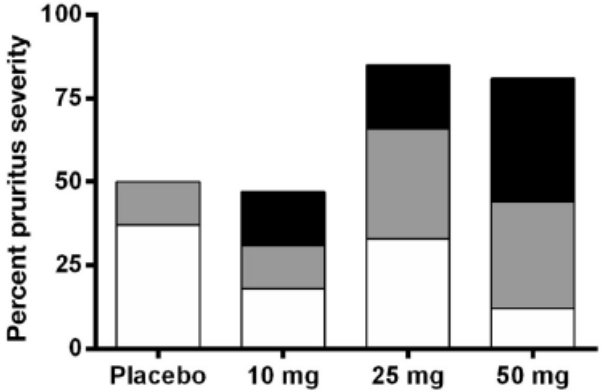


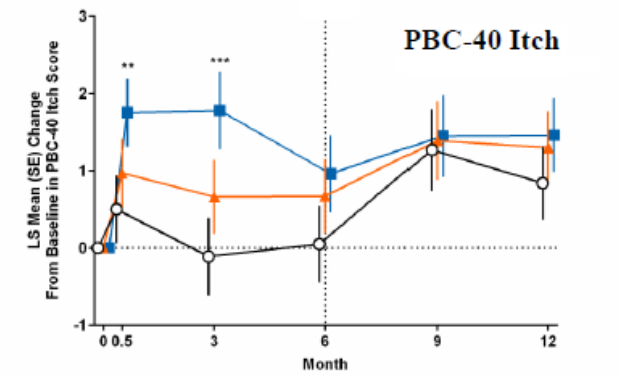


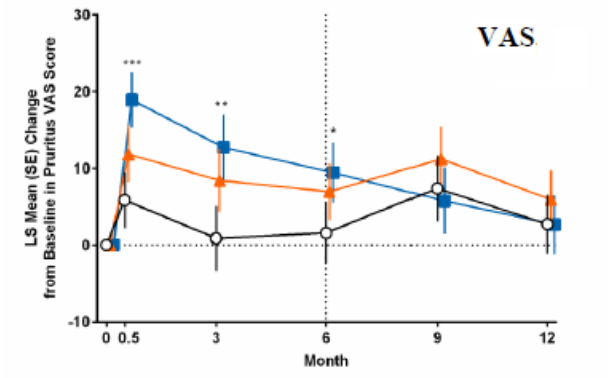


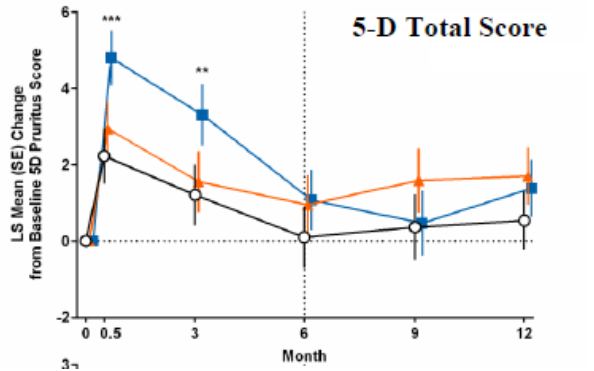
Hirschfield et al., 2015
Nevens et al., 2016

Pruritus and obeticholic acid



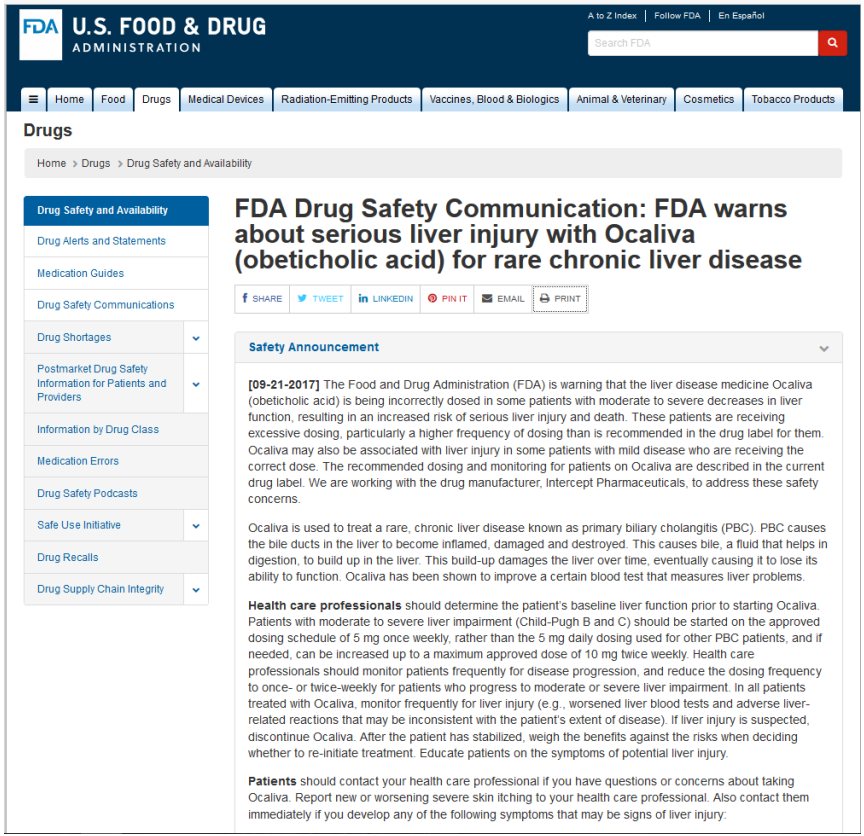






Hirschfield et al., 2015
Nevens et al., 2016

OCA in cirrhosis – FDA (September 2017)



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FDA Drug Safety Communication: FDA warns about serious liver injury with Ocaliva (obeticholic acid) for rare chronic liver disease

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Safety Announcement

[09-21-2017] The Food and Drug Administration (FDA) is warning that the liver disease medicine Ocaliva (obeticholic acid) is being incorrectly dosed in some patients with moderate to severe decreases in liver function, resulting in an increased risk of serious liver injury and death. These patients are receiving excessive dosing, particularly a higher frequency of dosing than is recommended in the drug label for them. Ocaliva may also be associated with liver injury in some patients with mild disease who are receiving the correct dose. The recommended dosing and monitoring for patients on Ocaliva are described in the current drug label. We are working with the drug manufacturer, Intercept Pharmaceuticals, to address these safety concerns.

Ocaliva is used to treat a rare, chronic liver disease known as primary biliary cholangitis (PBC). PBC causes the bile ducts in the liver to become inflamed, damaged and destroyed. This causes bile, a fluid that helps in digestion, to build up in the liver. This build-up damages the liver over time, eventually causing it to lose its ability to function. Ocaliva has been shown to improve a certain blood test that measures liver problems.

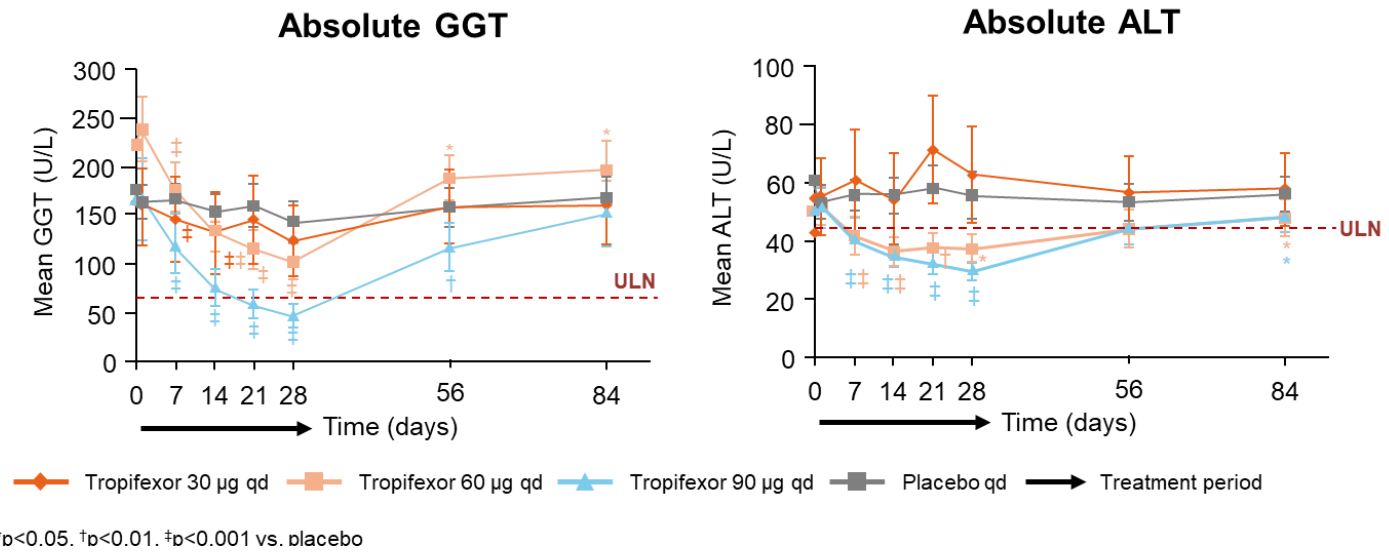
Health care professionals should determine the patient's baseline liver function prior to starting Ocaliva. Patients with moderate to severe liver impairment (Child-Pugh B and C) should be started on the approved dosing schedule of 5 mg once weekly, rather than the 5 mg daily dosing used for other PBC patients, and if needed, can be increased up to a maximum approved dose of 10 mg twice weekly. Health care professionals should monitor patients frequently for disease progression, and reduce the dosing frequency to once- or twice-weekly for patients who progress to moderate or severe liver impairment. In all patients treated with Ocaliva, monitor frequently for liver injury (e.g., worsened liver blood tests and adverse liver-related reactions that may be inconsistent with the patient's extent of disease). If liver injury is suspected, discontinue Ocaliva. After the patient has stabilized, weigh the benefits against the risks when deciding whether to re-initiate treatment. Educate patients on the symptoms of potential liver injury.

Patients should contact your health care professional if you have questions or concerns about taking Ocaliva. Report new or worsening severe skin itching to your health care professional. Also contact them immediately if you develop any of the following symptoms that may be signs of liver injury:

EMA dosing recommendation (February 2018)

Staging/Classification	**Non-Cirrhotic or** **Child-Pugh Class A**	**Child-Pugh Class B or C or** **Decompensated Cirrhotic**
Starting Dosage	**5 mg once daily**	**5 mg once weekly**
Dosage Titration	For patients who have not achieved an adequate reduction in alkaline phosphatase (ALP) and/or total bilirubin after **6 months** of treatment and the patient is tolerating obeticholic acid, titrate up to **10 mg once daily**	For patients who have not achieved an adequate reduction in ALP and/or total bilirubin after **3 months** of treatment and the patient is tolerating obeticholic acid, titrate up to **5 mg twice weekly** (at least 3 days apart) and subsequently to **10 mg twice weekly** (at least 3 days apart) based on response and tolerability
Maximum Dosage	**10 mg once daily**	**10 mg twice weekly** (at least 3 days apart)

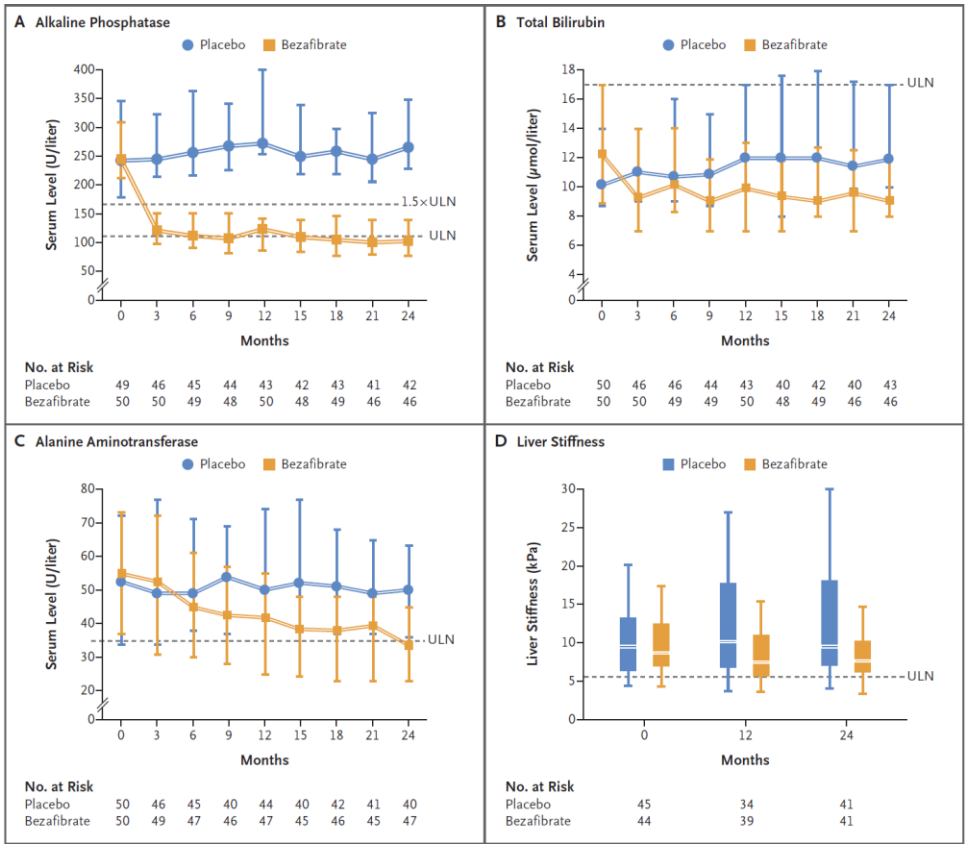
Tropifexor – non-bile acid FXR agonist



*p<0.05, †p<0.01, ‡p<0.001 vs. placebo

Schramm et al., EASL 2018

Bezafibrate (pan-PPAR agonist)



Corpechot et al., NEJM 2018

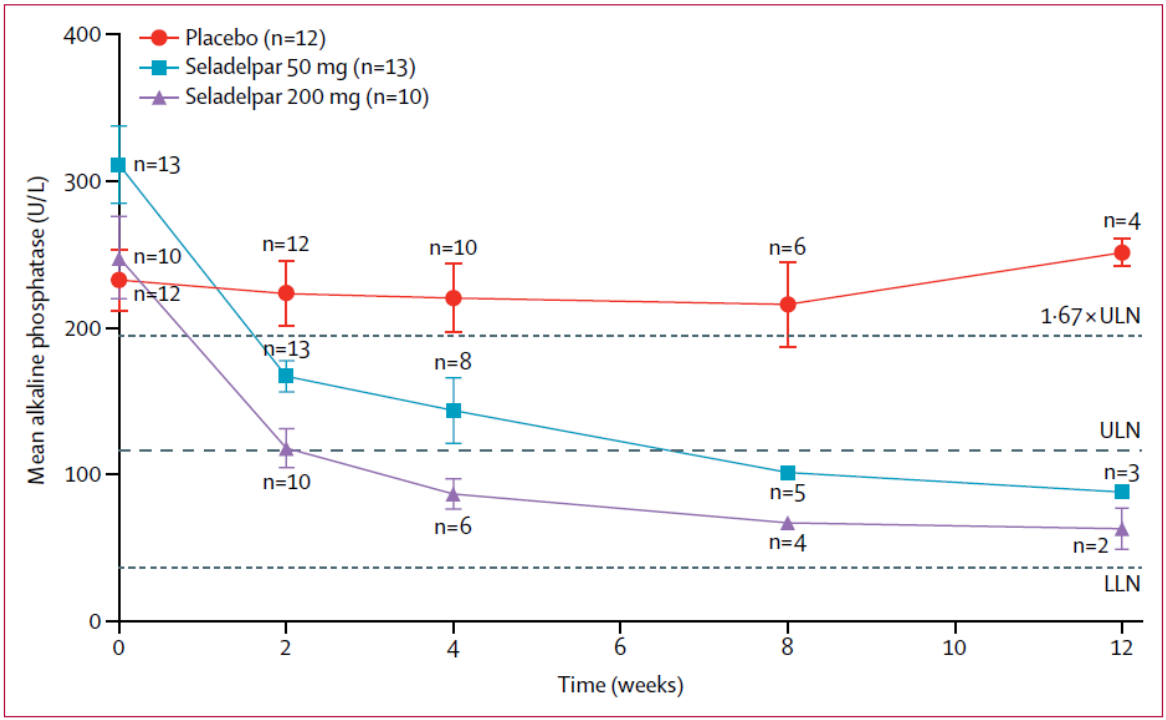
Bezafibrate (pan-PPAR agonist)

Table 3. Incidence of Adverse Events Occurring in 10% or More of Patients and All Serious Adverse Events.*

Event	Bezafibrate Group (N = 50)	Placebo Group (N = 50)
	no. of patients with event (%)	
Any adverse event	43 (86)	45 (90)
Arthralgia	7 (14)	11 (22)
Myalgia	10 (20)	5 (10)
Nasopharyngitis	9 (18)	10 (20)
Bronchitis	4 (8)	9 (18)
Depressive mood	7 (14)	8 (16)
Abdominal pain	7 (14)	6 (12)
Pruritus	4 (8)	7 (14)
Diarrhea	1 (2)	6 (12)
Flulike syndrome	5 (10)	5 (10)
Any serious adverse event	14 (28)	12 (24)
Aminotransferase level >5x ULN	3 (6)	1 (2)
Creatine kinase level >5x ULN	1 (2)	0
Creatinine increase with worsening stage of chronic kidney disease	1 (2)	0

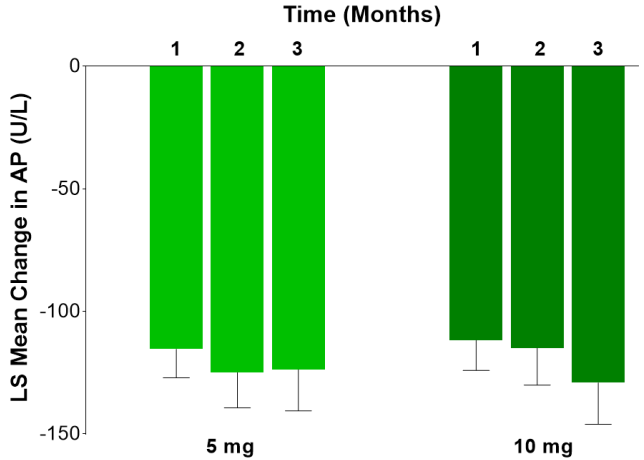
Corpechot et al., NEJM 2018

Seladelpar (selective PPARδ agonist)



Jones et al., 2017

Seladelpar (selective PPARδ agonist)



5 mg n = 12 (except for Month 3, n = 11)
10 mg n = 11
LS Mean ± SE
LS = Least Squares

No statistical differences between dose groups

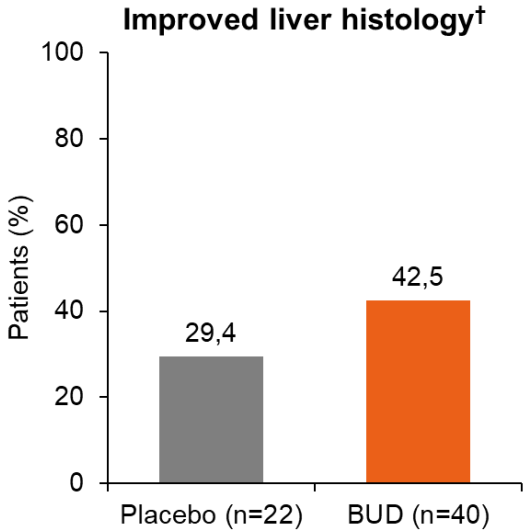
Hirschfield et al., AASLD 2017

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

*AP <1.67 x ULN, ≥15% decrease in AP, and total bilirubin ≤ ULN.

Hirschfield et al., AASLD 2018

Budesonide (GR and PXR agonist)



Improved liver function

Mean change from baseline (SD)	Placebo (n=40)	BUD (n=22)
ALT (U/L)	–0.16 (46.8)	–12.1 (30.2)
AP (U/L)	–8.9 (176.94)	–94.5 (166.3)
Total bilirubin (mg/dL)	0.59 (2.2)	–0.02 (0.4)

(Hirschfield et al., EASL 2018)

Symptoms management in PBC

The PBC Network

Primary biliary cholangitis (PBC)

Living with your diagnosis

Officially endorsed and reviewed by EASL

8 Managing your symptoms

It is possible to have PBC without knowing, but many people experience a number of symptoms, which may appear at any time and can affect your daily life.

Symptoms of PBC include:

- itching
- tiredness
- dry mouth, eyes and intimate areas (sicca complex)
- bone and joint pain
- stomach ache
- restless legs.

Treatment for your PBC will not alleviate your symptoms, but these can often be treated and improved if the right guidance is followed. Not all clinics and doctors will have expertise in treating PBC symptoms; this guide offers you advice on how best to manage them.

Please ask your doctor for advice if you experience any symptoms, or if your symptoms change. They may give you a questionnaire to fill in, to get a full picture of how PBC impacts your life.

How to deal with itching

Itching is a common symptom of PBC, although not all patients will have it. Indeed, some people may find that their itching improves while their condition worsens. Itching due to PBC can often be treated and improved, but there is no one-size-fits-all treatment. Instead, your doctor should look at your individual situation.

Your itching could be due to cholestasis, where the bile ducts in your liver are blocked. This could happen due to gallstones, or other complications from your condition. Itching may be especially strong if you have a form of PBC called 'ductopenic variant', where the bile ducts in your liver have disappeared.

There are medications available to help, but they may not be suitable or effective for everyone. Sometimes, a few practical measures can bring relief:

- Emollients and oatmeal extract can soothe dry and inflamed skin.
- Cold baths or showers may help, especially if your itching is triggered by heat.
- If scratching the itch has become an addiction and is damaging your skin, professional psychological advice can help.
- Consider whether food or other allergies could be the cause of your itching, rather than PBC, and ask your doctor to test for these if necessary.

Symptoms - patient involvement

27. EASL recommends treating pruritus using a step wise approach. Patients with severe pruritus may have an aggressively ductopenic variant of PBC, with a poor prognosis. EASL recommends the referral of these patients to an expert centre (**III**, **1**).

28. Given its favourable safety profile, EASL recommends cholestyramine as the first-line therapy for pruritus, despite its limitations. Attention should be paid to avoid interaction with other medications as a result of its anionic binding resin properties (**II-2**, **1**).

29. EASL recommends rifampicin as a second-line therapy for pruritus, usually at a dose of 150 mg–300 mg daily. EASL recommends monitoring serum liver tests after initial use (at 6 and 12 weeks following drug initiation) and following dose increase, because of potential hepatotoxicity The agent should be stopped if toxicity is observed (**II-2**, **1**).

Medications

There are several medications your doctor may prescribe to help with the itching. They all have advantages and disadvantages, and not every drug will work for you. They will usually be prescribed in the order listed below; be prepared to try more than one treatment, until you find the most effective option for you.

a) Bile sequestrants

These medications are often the first that your doctor will prescribe; they work by reducing the bile in your liver, if this is the cause of your itching. Here are some examples:

- Cholestyramine – this should be the first option that you are offered; although it does not work for all patients, most find that they don't have any problems taking it. Side effects that you may experience include bloating and constipation. It may also be affected by other medications you are taking – always discuss this with your doctor.
- Colesevelam – this produces less side effects but its effectiveness is uncertain. Some people feel better when taking it, and tests have shown that it has reduced their bile acid levels. On the other hand, this medicine did not work better than a placebo in a controlled trial.

If you take bile sequestrants, you should be aware that:

- they might stop other drugs from working if you take them at the same time
- you must take them 2 to 4 hours before you take any other drug, such as UDCA or OCA.

Ask your doctor for advice on when exactly to take your medicines.

b) Antibiotics

If bile sequestrants do not help your itching then your doctor may prescribe rifampicin, an antibiotic that treats bacterial infections. It can improve itching in PBC by inhibiting a receptor in your body that is thought to play a role in itching. The recommended dose is 150–300mg daily.

We know from clinical trials that rifampicin really works against itching in PBC, and also in other cholestatic diseases. Unfortunately, it can cause side effects, although not everybody gets them. These are not included in the EASL PBC guidelines, but include nausea, vomiting, diarrhoea, loss of appetite, and high body temperature. You may also find that some of your bodily fluids, such as urine, sweat and tears, change colour to orange-red. Don't let this scare you – this effect is common and looks strange, but should not cause concern. Rifampicin may also lower the amount of vitamin K in your body.

Some patients may experience more serious side effects, such as fewer red blood cells, longer blood clotting, or even liver damage. If you take rifampicin, your doctor will order regular blood tests for monitoring; this should take place after 6 weeks and again after 12 weeks. If this detects any new problems, you may need to stop taking rifampicin and try something else.

c) Oral opiate antagonists

If bile sequestrants and/or rifampicin do not work for you, or produce too many side effects, oral opiate antagonists may be another option. These include naltrexone and nalmefene, which can reduce itching but may also have long-term side effects.

Starting naltrexone on a low dose will help to avoid these side effects, which can be similar to those of opiate withdrawal and feel a bit like flu. You may also be more sensitive to pain.

Complications - patient awareness

34. EASL recommends considering the risk for osteoporosis in all patients with PBC (**III, 1**).
35. As part of evaluating the risk of osteoporosis, EASL recommends considering the use of DEXA to assess bone mineral density at presentation and at follow-up where indicated (**III, 1**).
36. EASL suggests supplementing patients with PBC with calcium and vitamin D, according to local practice (**III, 2**).
37. Bisphosphonates are safe and effective treatments for patients with PBC and significantly elevated fracture risk from osteoporosis but EASL recommends caution when using them in patients with varices. EASL recommends therapy initiation following specific osteoporosis guidelines (**II-2, 1**).

38. Fat-soluble vitamin malabsorption can occur in patients with PBC, particularly those with prolonged jaundice. EASL suggests that supplementation should be considered on an individual basis (**III, 2**).

39. Hyperlipidemia is a feature of cholestasis, for which there is no substantial evidence to support an elevated cardiovascular risk in patients with PBC. In the subgroup of patients with PBC and metabolic syndrome (with high cholesterol, low HDL cholesterol and high LDL cholesterol levels), EASL suggests considering a pharmacologic approach with cholesterol-lowering agents on a case-by-case basis; treatment is not contraindicated (**III, 2**).

40. EASL suggests that the Baveno-VI guidelines for screening and management of varices apply equally to patients with PBC (**III, 2**).

PBC can lead to a number of complications. Your doctor can help you manage these in a variety of ways.

Osteoporosis

Osteoporosis is a bone disease that occurs when the body loses too much bone, makes too little bone, or both. As a result, bones become weak and may break from a fall or, in serious cases, from sneezing or minor bumps.

Osteoporosis is a common complication in patients with PBC. You can help to prevent and treat osteoporosis by ensuring you have a good diet, take some weight-bearing exercise, and stop smoking. Your doctor may consider giving you calcium supplements (if you have no history of renal stones) and vitamin D. Several trials have demonstrated that bisphosphonates (drugs that prevent or slow down bone thinning), especially weekly alendronate and monthly ibandronate, are effective in increasing bone mass in patients with PBC.

Reduced vitamin absorption

Patients with PBC, particularly those with prolonged jaundice, can struggle to absorb fat-soluble vitamins (vitamins A, D, E and K). Your doctor may recommend that you take a supplement, but this should be considered on an individual basis.

Hyperlipidaemia

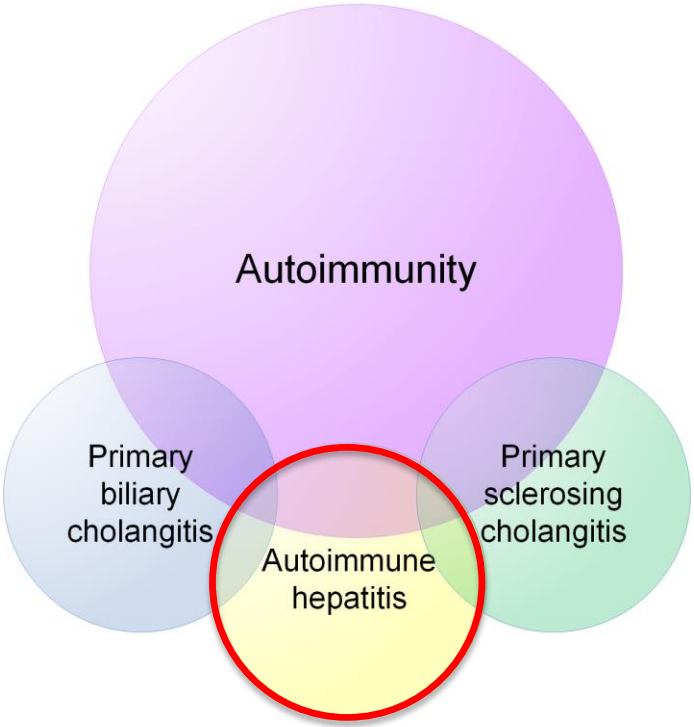
When the concentration of triglycerides or cholesterol in your blood is too high, it is called 'hyperlipidaemia'. Hyperlipidaemia is normally linked to an increased risk of cardiovascular disease, such as heart attack and angina, stroke, and narrow blood vessels in the legs. But it can also appear because of cholestasis, as part of your PBC, so it does not necessarily mean that your cardiovascular risk is increased.

If you have PBC alongside low HDL cholesterol and high LDL cholesterol levels, we recommend that you take cholesterol-lowering medication as part of a personalised plan.

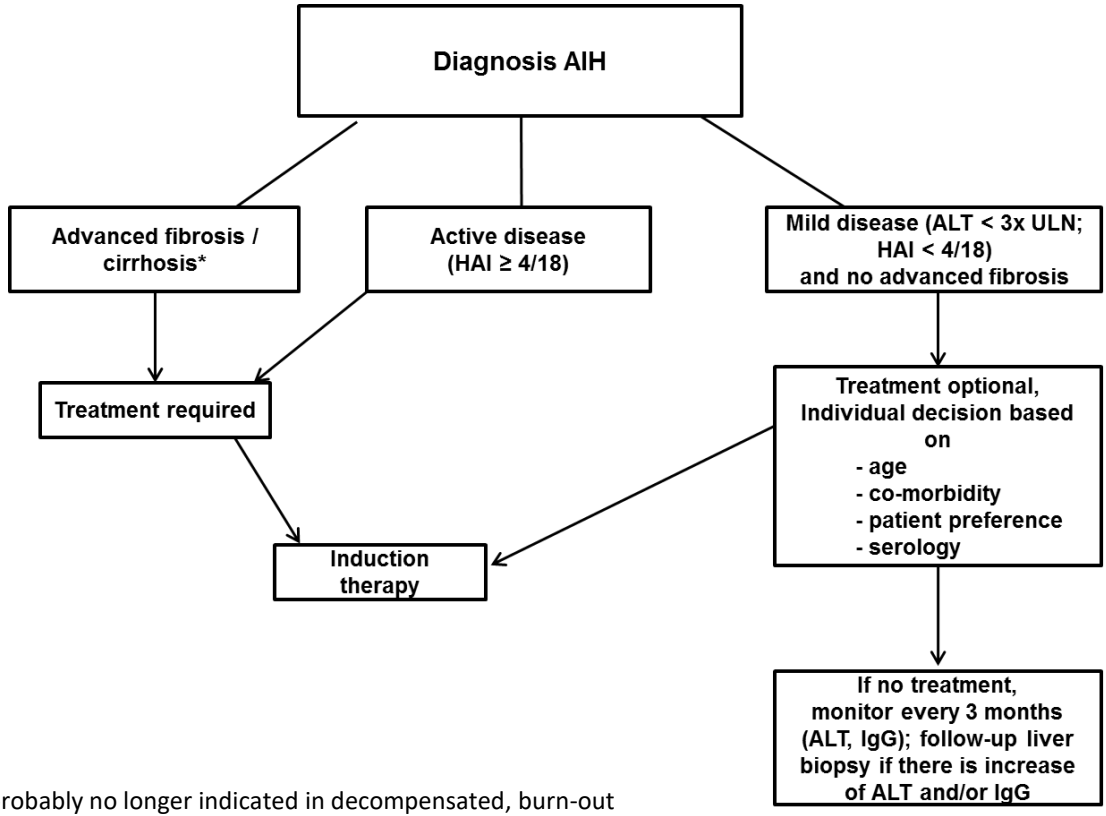
Veins

Patients with PBC may develop a type of high blood pressure known as 'portal hypertension'. This affects your hepatic portal system, which is the part of your vein network that directs blood from your intestines to your liver. Portal hypertension is often caused by scar tissue (cirrhosis) that forms in your liver due to inflammation.

Autoimmune hepatitis

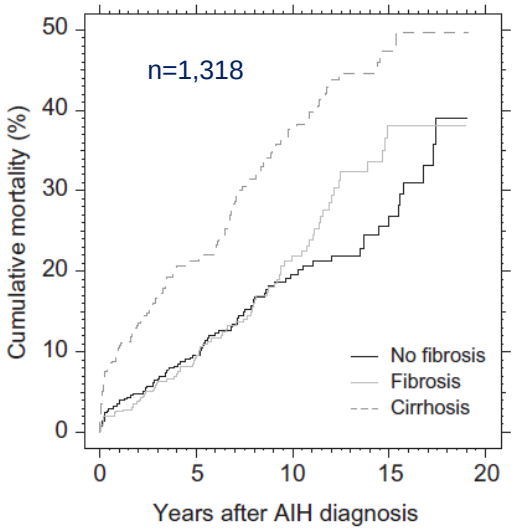


Standard management in AIH



*Treatment probably no longer indicated in decompensated, burn-out cirrhosis, unless high inflammatory score on liver biopsy

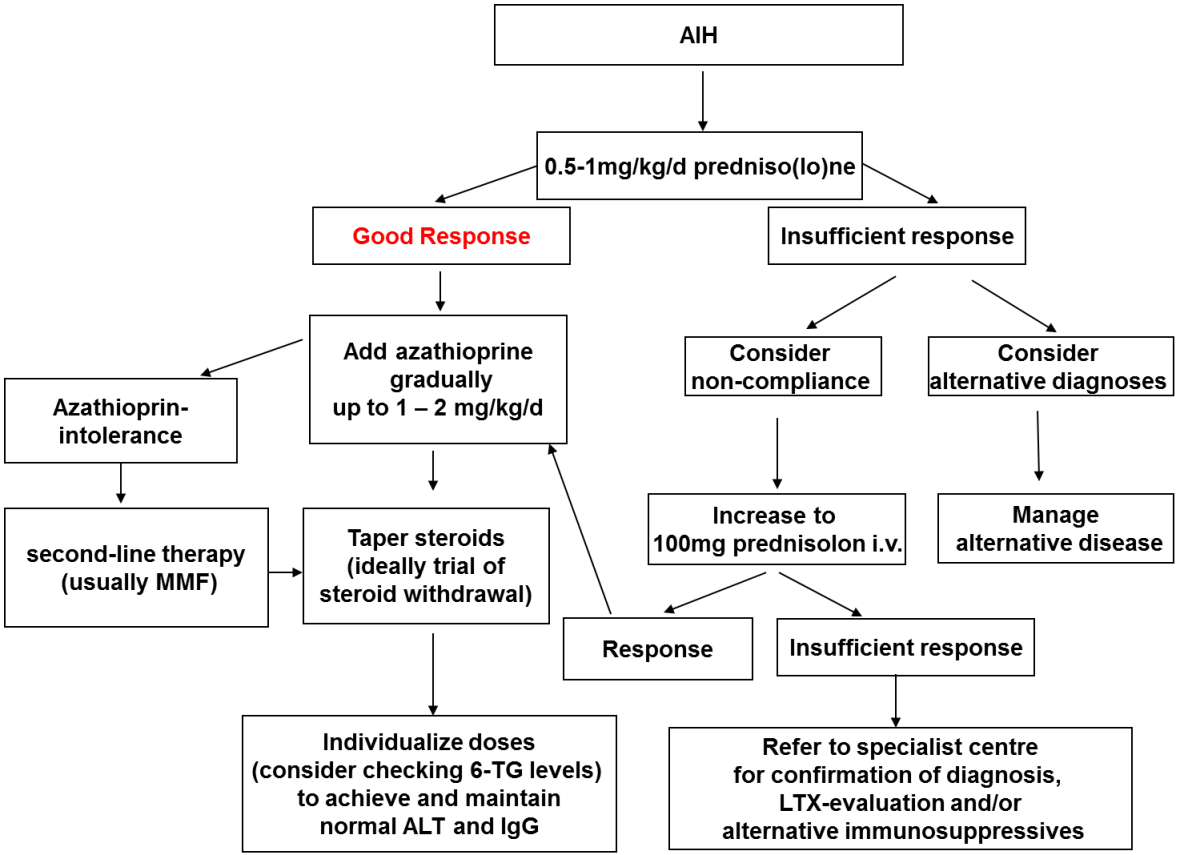
Liver cirrhosis at presentation?



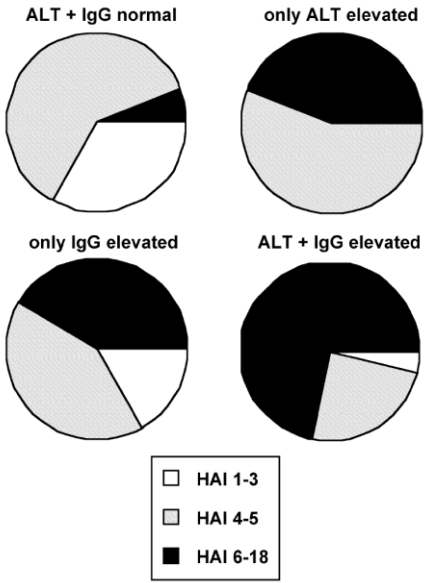
Gronbaek et al., 2014

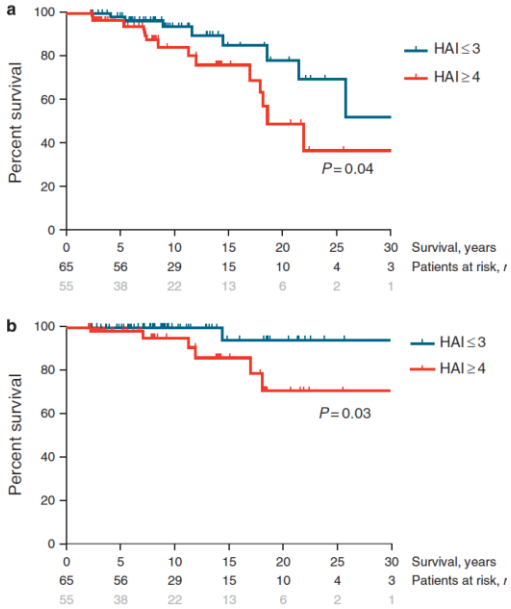
- **Subclinical disease preceding diagnosis**
- **1/3 adults and 1/2 children cirrhosis at diagnosis**
- **Response in cirrhosis similar, but slower?**
- **Decompensated cirrhosis? (consider HAI)**

Standard management in AIH



Treat to what end-point?

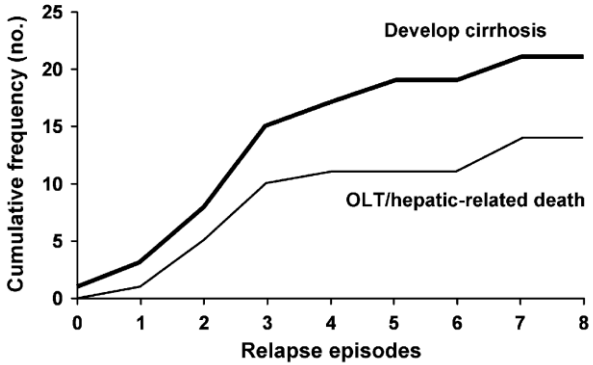




- **Biochemical remission: normalization of IgG and transaminases**
- **Histological remission: normal histology or HAI < 4 or equivalent**

Luth et al., 2008
Dhaliwal et al., 2015
www.easl.eu

Withdrawal of treatment ?



- Treatment >3 years and >2 years following biochemical remission
- A liver biopsy should be considered prior to treatment withdrawal
- In patients with HAI>3, treatment should not be discontinued
- Surveillance continued life-long (frequently during first 12 months)
- 50-90% of the patients relapse (depending on observation time)
- If relapse occurs, life-long immunosuppression advisable

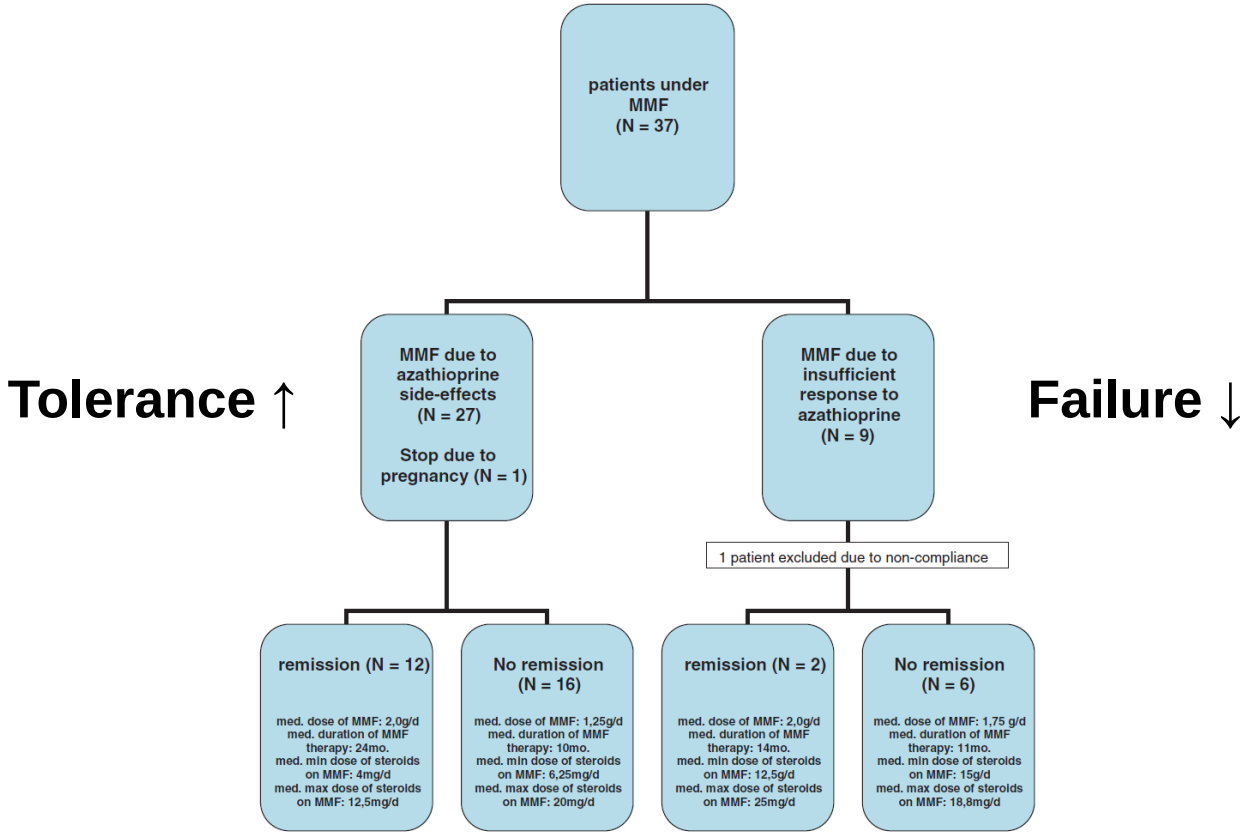
Montano-Loza et al., 2007

„Difficult to treat“ AIH

- Intolerance to treatment
  - Azathioprine: Prednisolone monotherapy? Mycophenolate?
  - Prednisolone: Budesonide?
  - Referral for individualized therapy

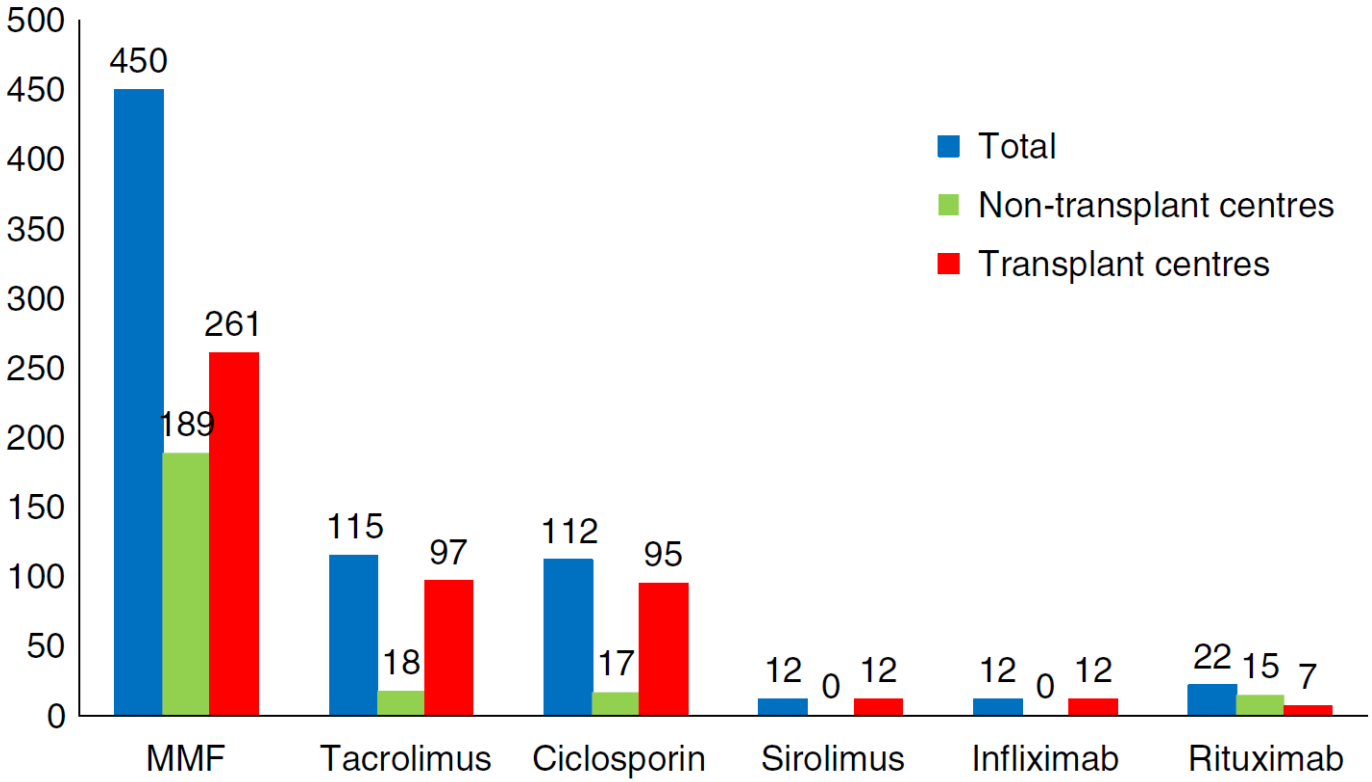
- Incomplete response
  - Consider diagnosis, concomitant liver disease?
  - Consider compliance (e.g. 6TGN)
  - Increasing the dose of azathioprine to 2 mg/kg/day?
  - Referral for individualized therapy (e.g. CNI, infliximab)
  - Complete response may not be attainable in some patients

Principles of 2nd line therapy



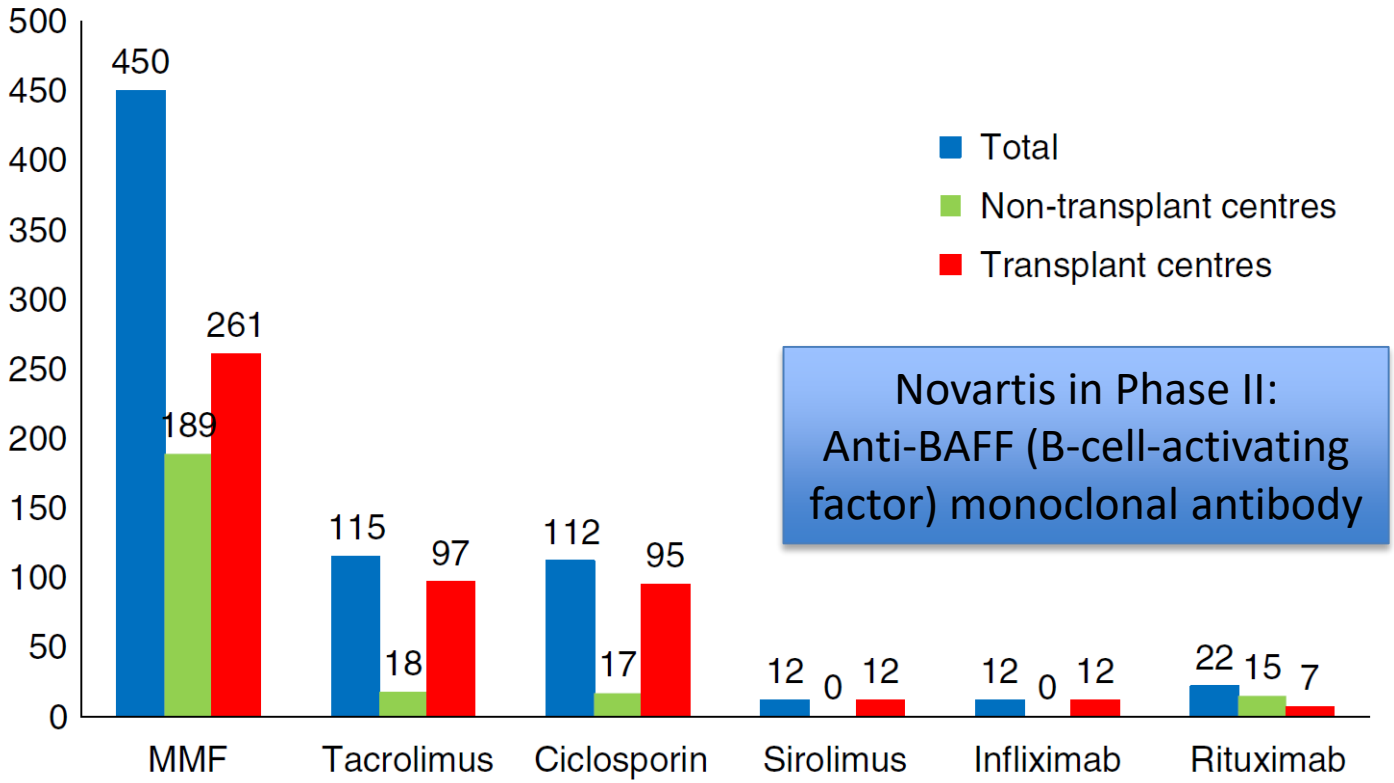
Hennes et al., 2008

Survey – 2nd line (IAIHG)



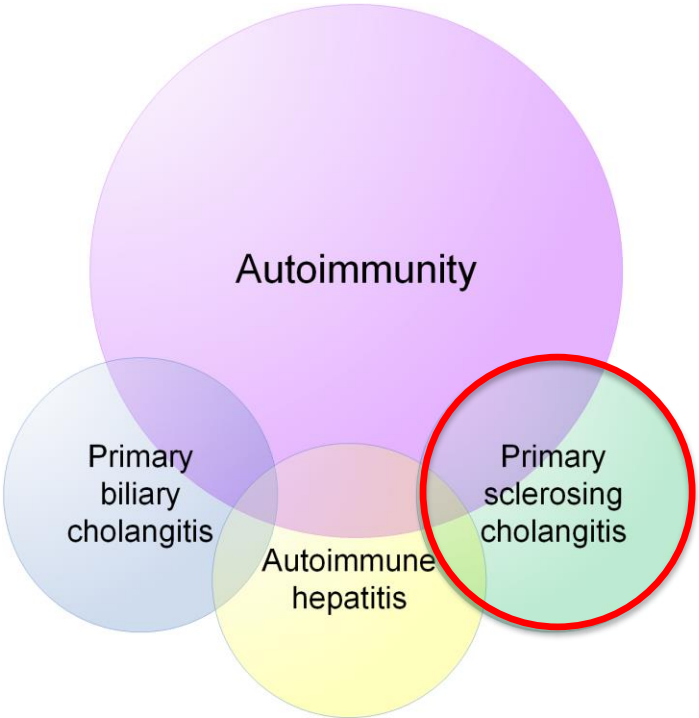
Liberal et al., 2017

Survey – 2nd line (IAIHG)

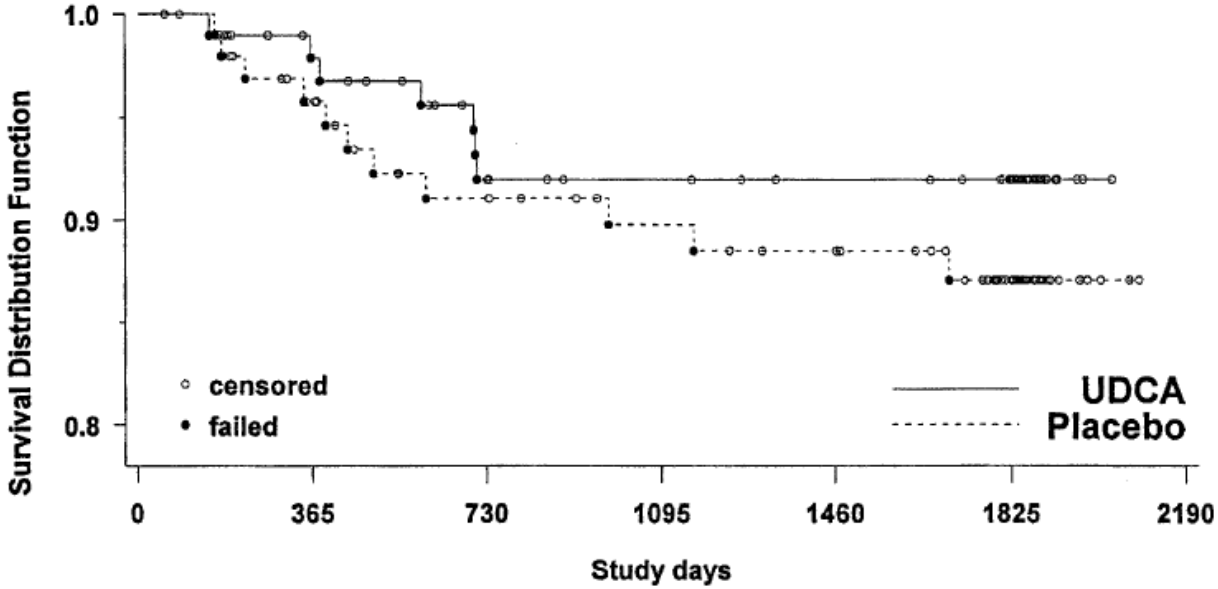


Liberal et al., 2017

Primary sclerosing cholangitis

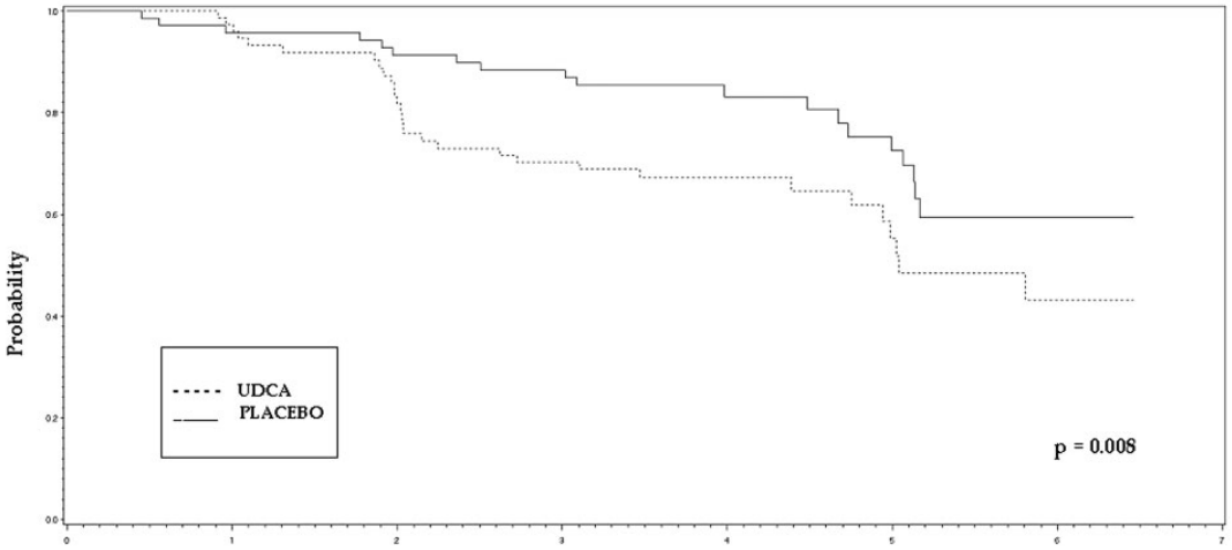


Is ursodeoxycholic acid helpful in PSC?



(Olsson et al., 2005)

Is ursodeoxycholic acid harmful in PSC?

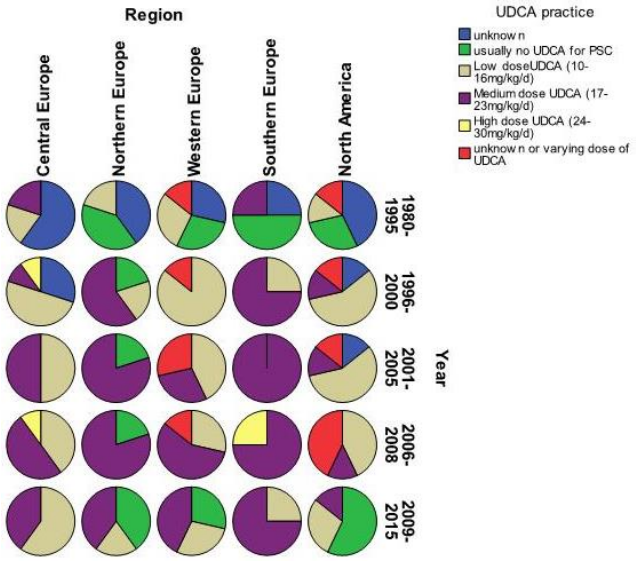


Number at Risk								
UDCA	76	73	60	51	34	18	9	0
PLACEBO	74	65	60	58	41	24	7	0

(Lindor et al., 2009)

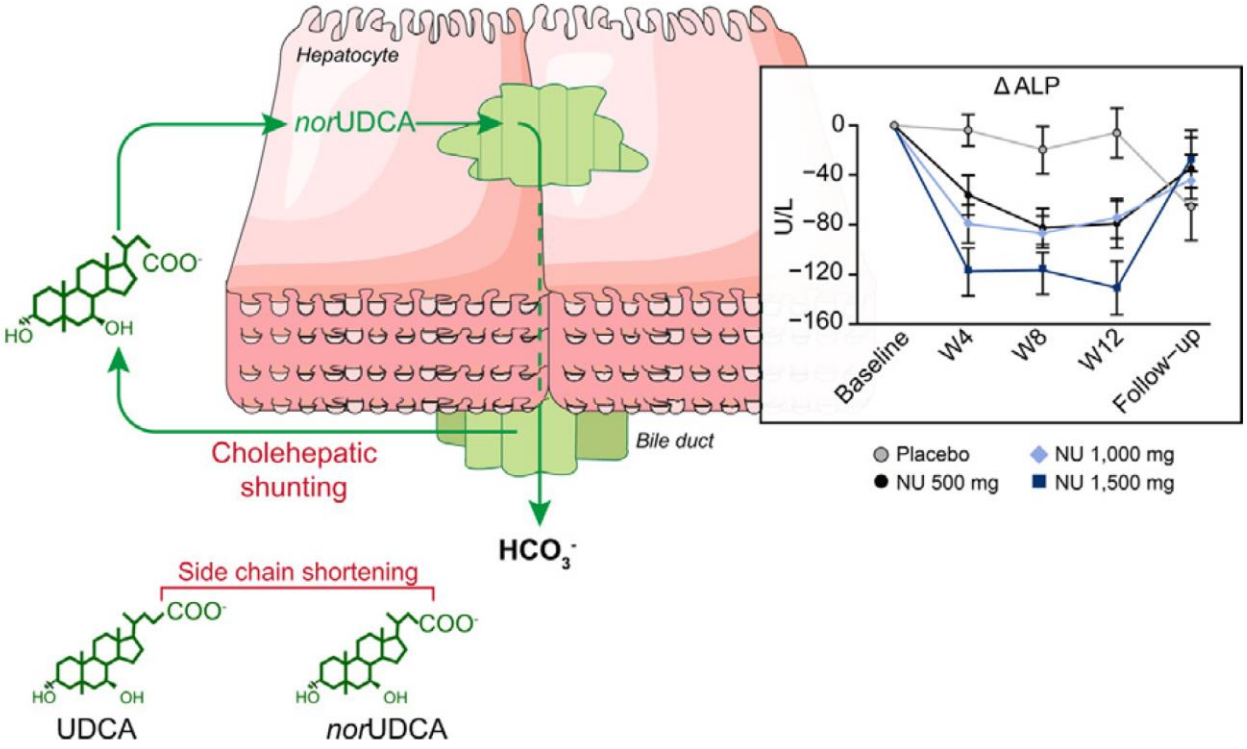
Ursodeoxycholic acid in PSC?

Study	Year	Dose (mg/kg bw/ day)	N (treat/ control)	Study duration	Lab	Histology	CCA	OLT-free survival	Outcome
O'Brien *et al.*[49]	1991	10	12*	2.5 years	+	ND	ND	ND	Improvement of liver tests in treatment periods and worsening in nontreatment periods
Beuers *et al.*[50]	1992	13–15	14 (6/8)	1 year	+	+	ND	ND	Significant improvement in liver biochemistry
Stiehl *et al.*[51]	1994	750/day†	20 (10/10)	3 months	+	ND	ND	ND	Significant improvement in liver tests
De Maria *et al.*[52]*	1996	300 b.d.†	40 (20/20)	2 years					No effect on liver tests or cholangiography
Lindor *et al.*[53]	1997	13–15	102 (51/51)	2.2 years	+	–	ND	–	No significant effect on primary end-points (death, OLT, histology, lab)
Mitchell *et al.*[54]	2001	20	26 (13/13)	2 years	+	+	ND	ND	UDCA group had improved liver test results, histology and cholangiography
Harnois *et al.*[55]	2001	25–30	30‡	1 year	+		ND	ND	Improved Mayo Risk Score for UDCA vs. placebo and for high-dose vs. low-dose UDCA Improved liver test results
Olsson *et al.*[56]	2005	17–23	198 (97/101)	5 years	(+)	ND	–	–	No effect on death, OLT, CCA or liver tests
Lindor *et al.*[57]	2009	28–30	149 (76/73)	6 years	+		ND	–	Terminated at 6 years as worse outcome in treatment group for death or OLT Improved liver tests in UDCA group



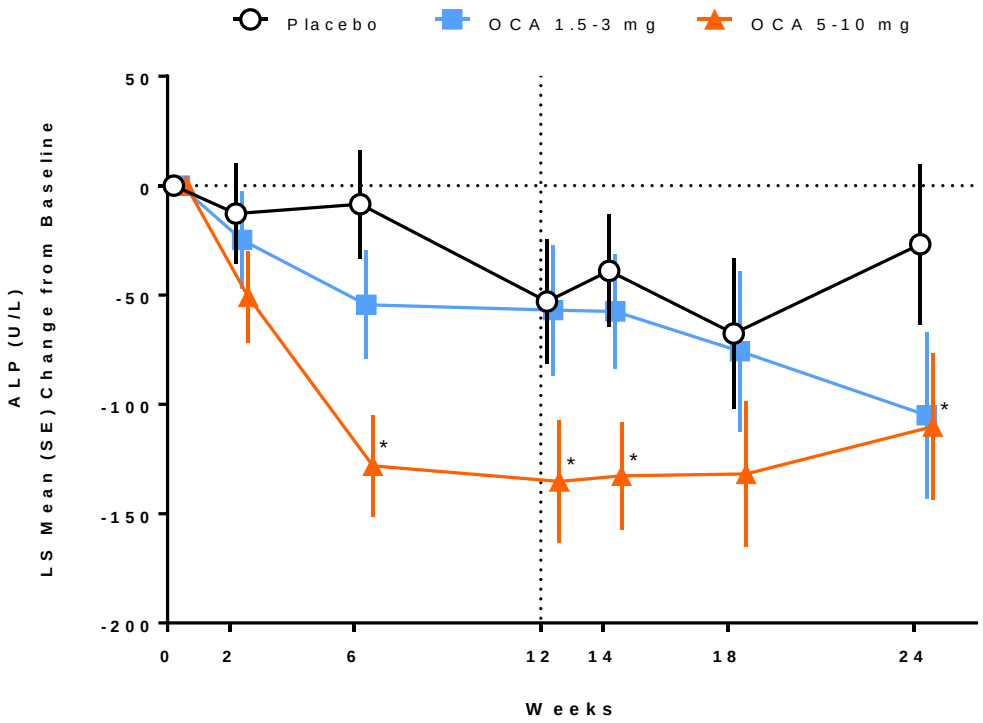
(Karlsen et al., AP&T 2014, IPSCSG survey)

norUDCA in PSC



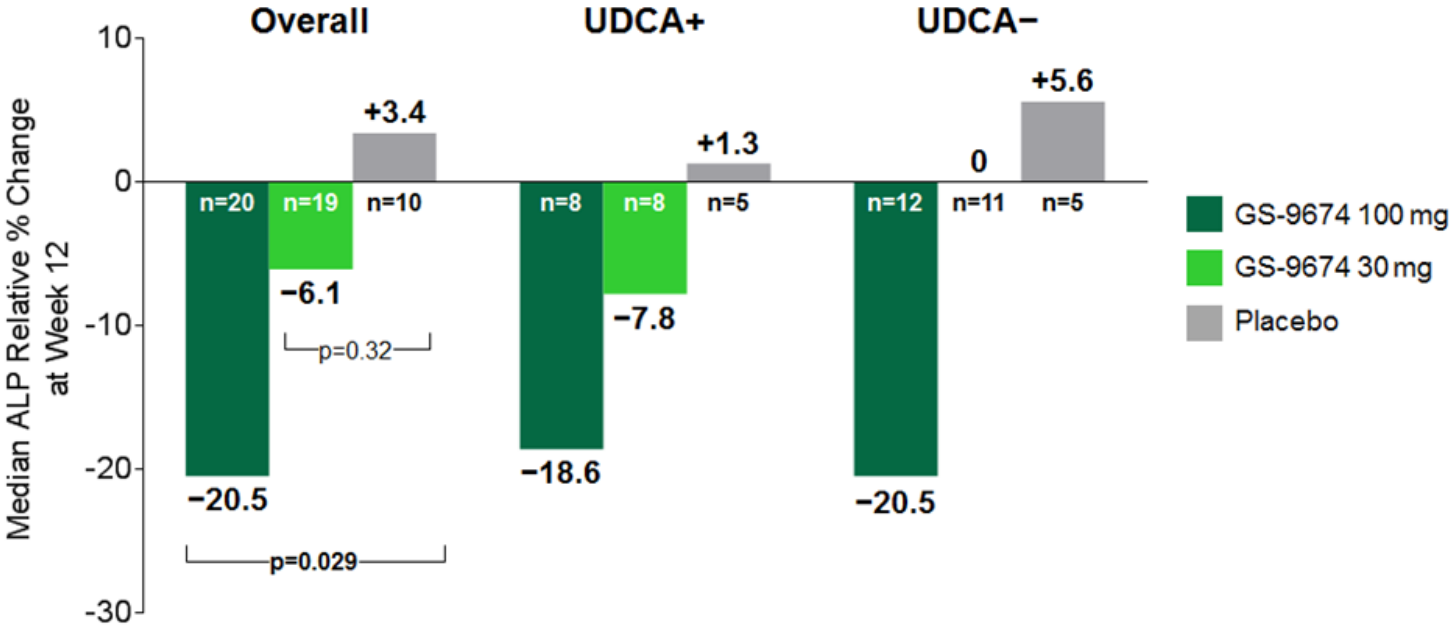
Trauner et al., JHEP 2017

Obeticholic acid in PSC



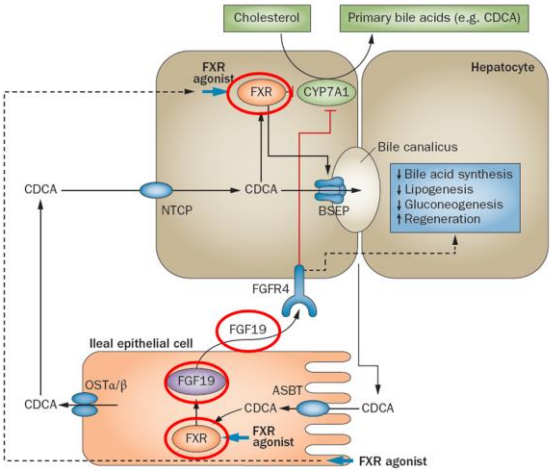
Cowdley et al., AASLD 2017

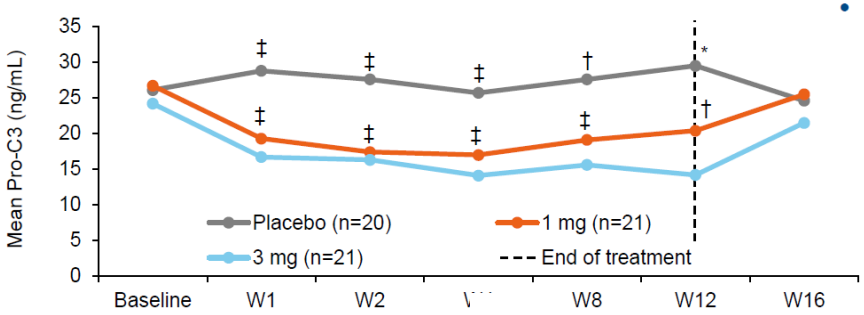
GS-9674 in PSC (non-steroidal FXR)



Trauner et al., AASLD 2018

NGM282 in PSC (FGF19 analog)

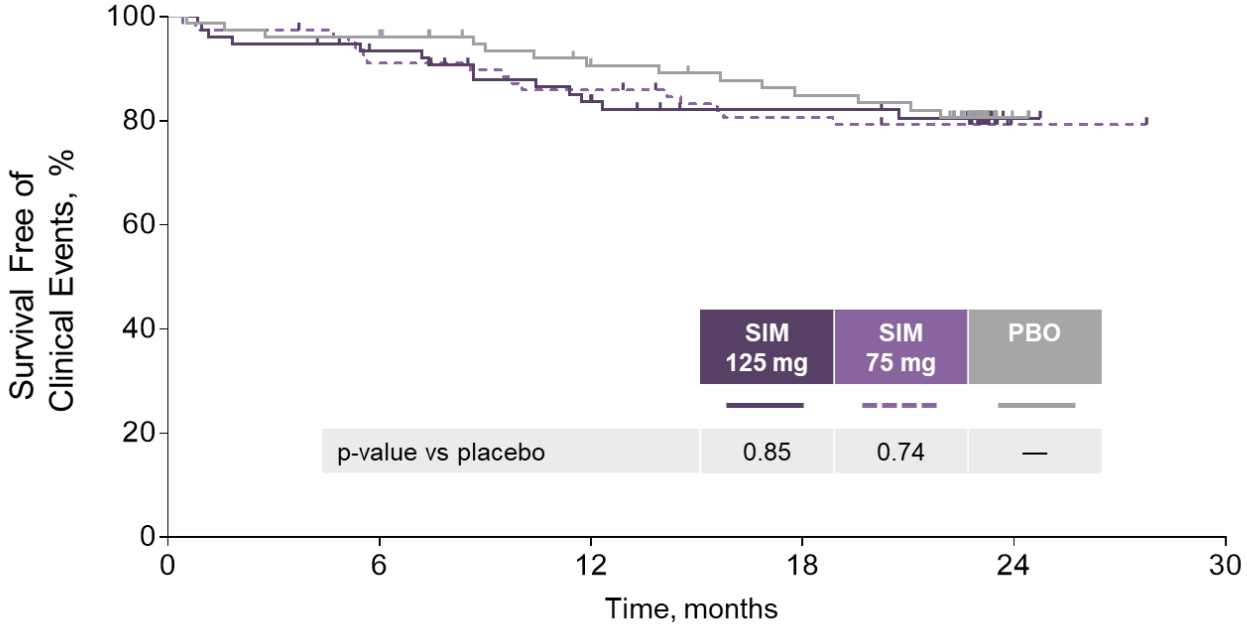




	Placebo (n=20)			NGM282 1 mg (n=21)			NGM282 3 mg (n=21)		
	Day 1	Week 12	p	Day 1	Week 12	p	Day 1	Week 12	p
Mean AP (U/L)	365	355	0.78	383	409	0.22	354	351	0.73
Mean ALT (U/L)	90	86	0.26	117	114	0.41	96	56	<0.001
Mean change in ELF score from baseline	**Placebo**			**NGM282 1 mg**			**NGM282 3 mg**		
From baseline of ≤9.8	0.08			0.12 (p=0.90 vs. placebo)			–0.24 (p=0.23 vs. placebo)		
From baseline of >9.8	–0.01			–0.52 (p=0.016 vs. placebo)			–0.58 (p=0.029 vs. placebo)		

Hirschfield et al., EASL 2018

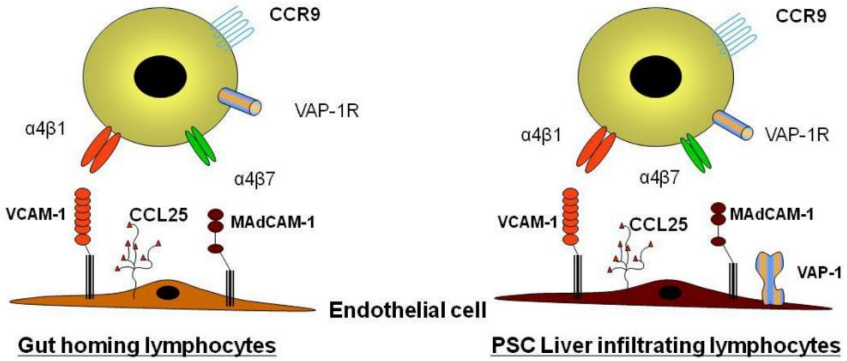
Simtuzumab phase II data

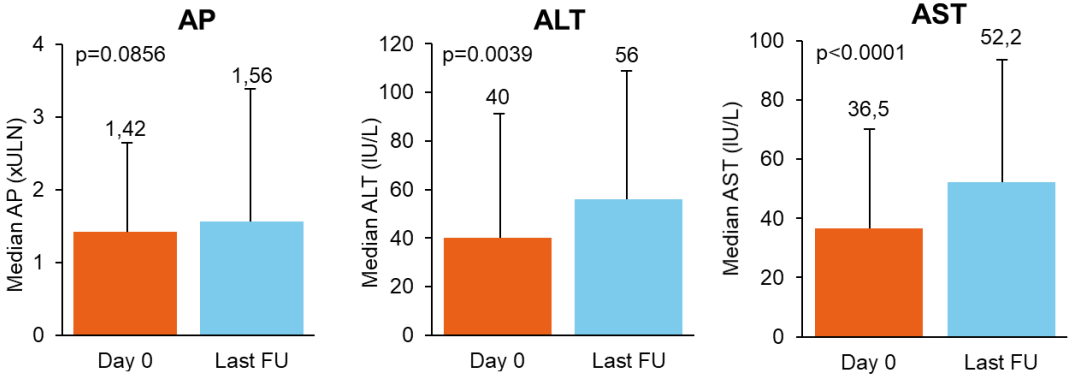


Number at risk (n)						
Placebo	78	75	64	59	1	0
SIM 125 mg	77	69	57	52	2	0
SIM 75 mg	79	71	67	61	1	0

Muir et al., EASL 2017

Vedolizumab real life data in PSC





Williamson et al., EASL 2018

Antibiotics in PSC – therapy or proof-of-concept?

(a) Clinical trials of antibacterial treatment in primary sclerosing cholangitis

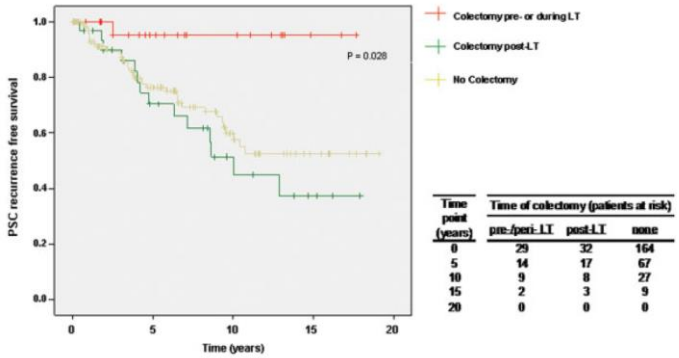
Drug (reference)	Year	n	Antibiotic dose	Months of therapy	Change after therapy		
					ALK	AST	ALT
Metronidazole (+UDCA) [34]	2004	39	600–800 mg/day	36	−52.4%	−41.0%	−67.9%
Minocycline [35]	2009	16	200 mg/day	12	−19.7%	−2.8%	NA
Vancomycin or metronidazole [25]	2013	18	Vancomycin 125 or 250 mg qid	3	−42%	−22%	NA
		17	Metronidazole 250 or 500 mg tid	3	−10%	−9%	NA

(b) Case series and reports of antibacterial treatment in primary sclerosing cholangitis

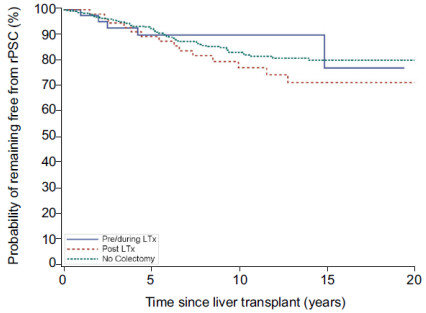
Drug (reference)	Year	n	Antibiotic dose	Months of therapy	Change after therapy		
					ALK	AST	ALT
Tetracycline [36]*	1959	5	500 mg/day	1–10	−45%	−60%	−45%
Tetracycline [27]†	1965	5	500 mg/day	48 (mean)	−21%	NA	NA
Metronidazole [37]	1983	1	800 mg/day	0.25	NA‡‡	NA‡‡	NA‡‡
Sulfasalazine (+UDCA) [38]††	1998	2‡	—	30 and 45	−79% −35%	−38% −87%	−70% −95%
Vancomycin [39]	1998	3‡	375–1000 mg/day	9 (mean)	NA	NA	−89%
Sulfasalazine (+UDCA) [40]	2002	1	50 mg/kg/day	37	NA	NA	−92%
Sulfasalazine [41]	2006	1	2–4.5 g/day	24	−74%	NA	−84%
Azithromycin (+UDCA) [42]	2007	1	500 mg/day, 3 days/week	5	−72%	−31%	−33%
Vancomycin [43]	2008	14‡	50 mg/kg/day	54 ± 43	NA	NA	−78%

(Tabibian et al., 2013)

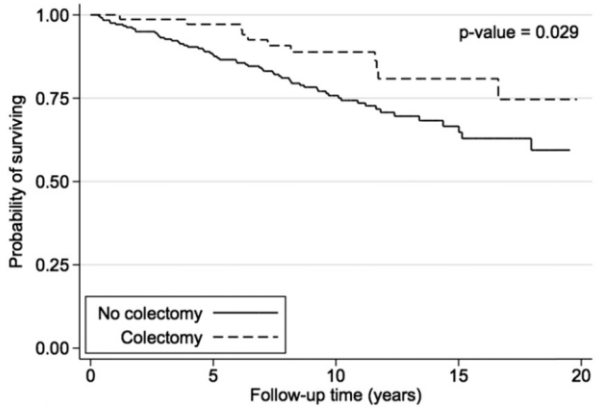
Recurrent PSC – role of the colon?

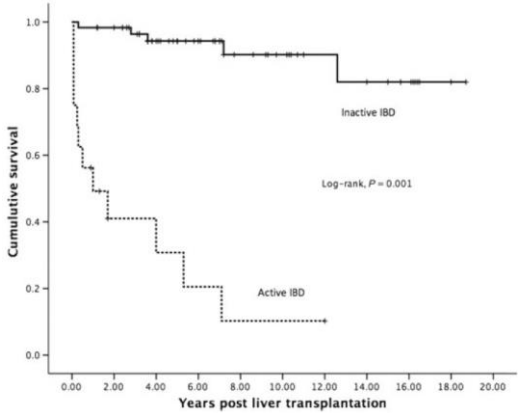


Time point (years)	Time of colectomy (patients at risk)		
	pre-/peri- LT	post-LT	none
0	29	32	164
5	14	17	67
10	9	8	27
15	2	3	9
20	0	0	0



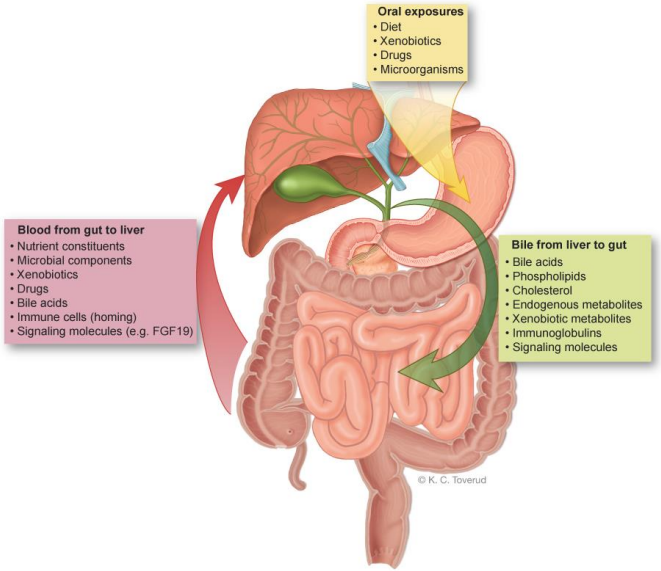
Hazard ratio's
Post-LTx colectomy *vs.* Pre-LTx colectomy = 1.89 (0.61, 5.81)
No colectomy *vs.* Pre-LTx colectomy = 1.23 (0.50, 3.06)

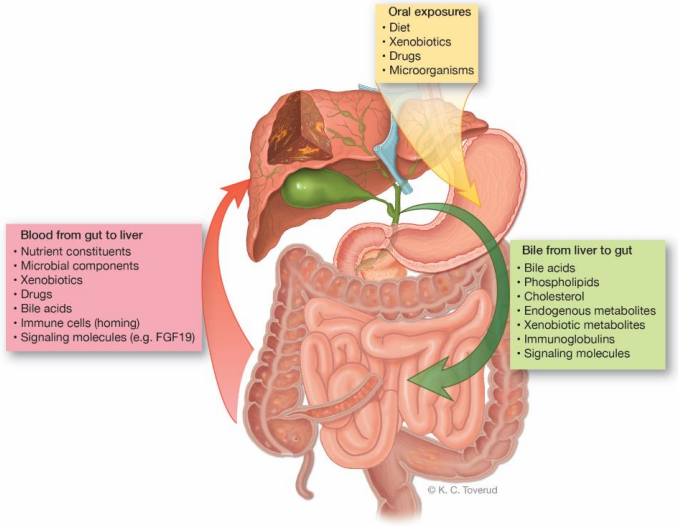




(Alabraba et al. 2009, Ravikumar et al. 2015, Lindström et al. 2018 Joshi, et al., 2011)

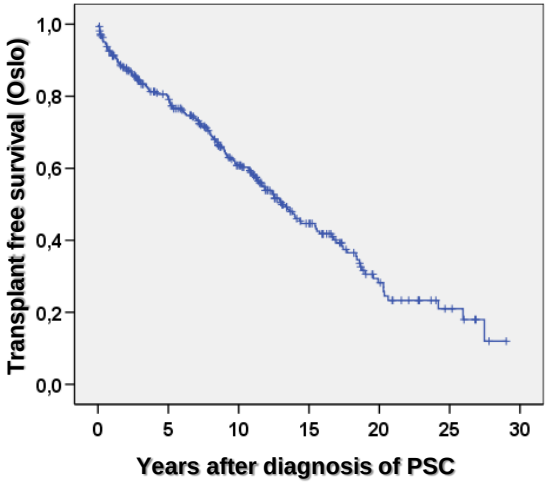
PSC as a model disease for gut-liver interactions

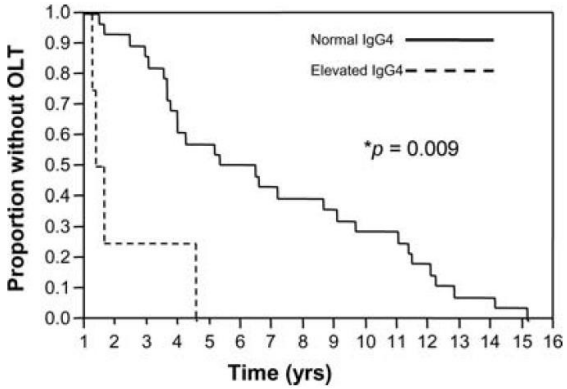


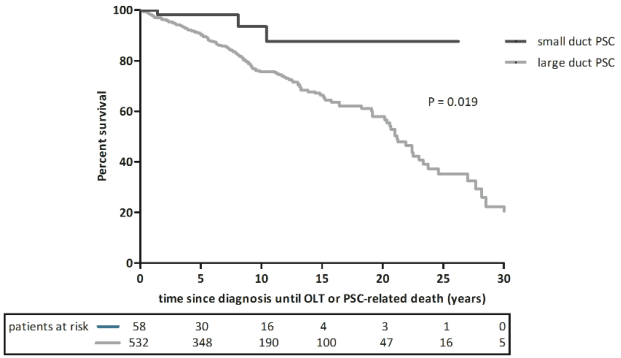


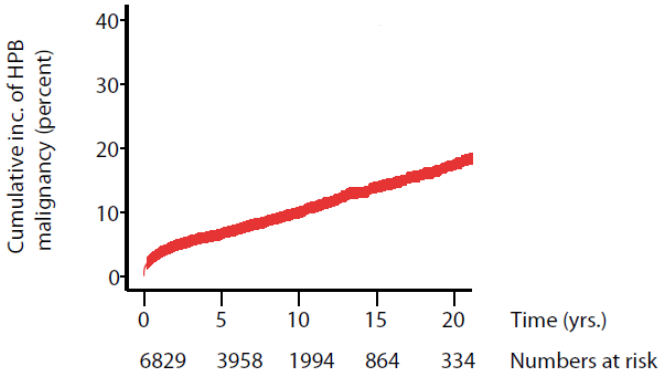
(Hov and Karlsen, Semin Liv Dis 2017)

Four important Kaplan-Meier plots for PSC



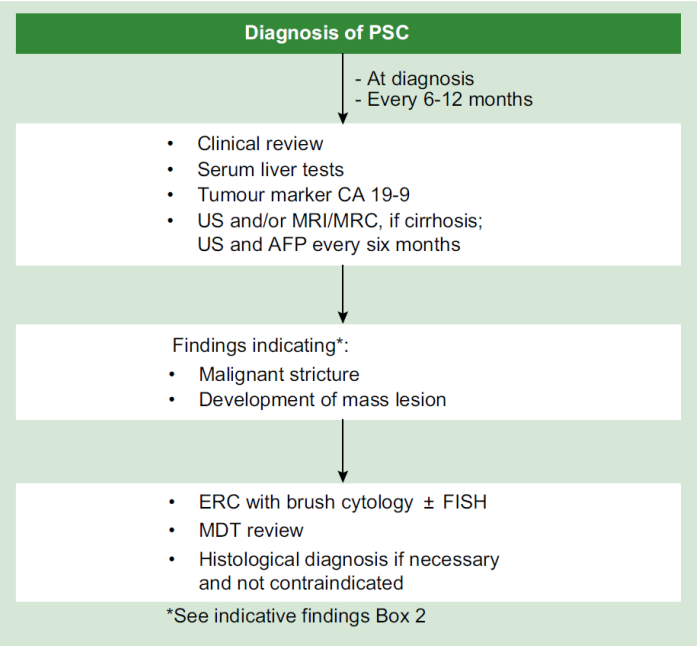






(URQ – Oslo, ULQ – IPSCSG, LRQ – Mendes et al. 2008 , LLQ – Boonstra et al. 2013)

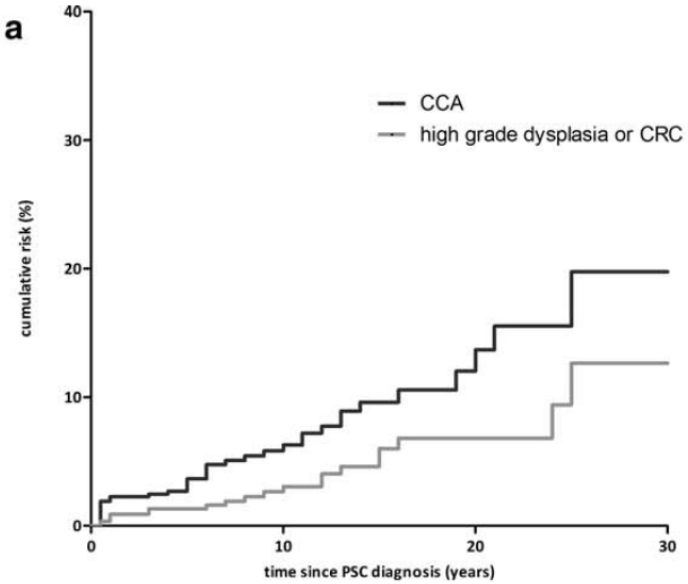
Cholangiocarcinoma surveillance

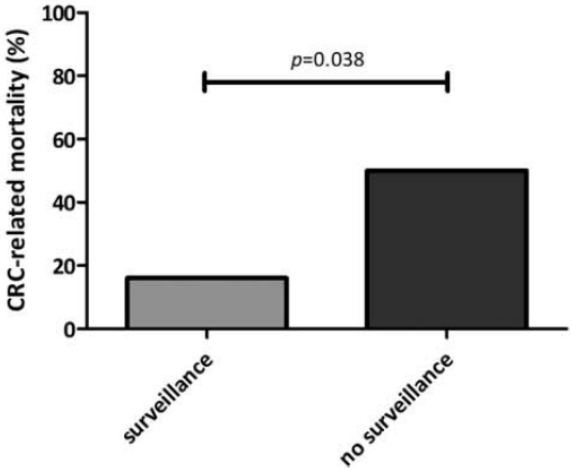


Diagnostic features	Cholangiocarcinoma	Bile duct dysplasia
Indicative findings		
1. Clinical:	• Rapid clinical deterioration (features of biliary obstruction, weight loss, abdominal pain)	• None
2. Biochemical:	• Cholestatic liver function tests • Continuously elevated CA19-9 after biliary decompression • Elevated CA-125 (65%)	• None
3. Non-invasive imaging (MRI/MRC, CT, US)	• Mass lesion (iCCA) Hilar stricture (pCCA) Distal bile duct stricture (dCCA) ± biliary duct dilatation, extrahepatic metastasis	• Bile duct stricture
4. Invasive imaging: (ERC, POCS, IDUS)	• Bile duct stricture or polypoid lesion	• Bile duct stricture
Confirmatory findings		
5. Cytological: ± DIA or FISH	• High grade dysplasia or carcinoma • Cellular aneuploidy	• Low to high grade dysplasia
6. Histological: (FNAC, biopsy, surgical specimens)	• Carcinoma (adenocarcinoma >95% of cases)	• Low to high grade dysplasia

(Karlsen et al., 2017)

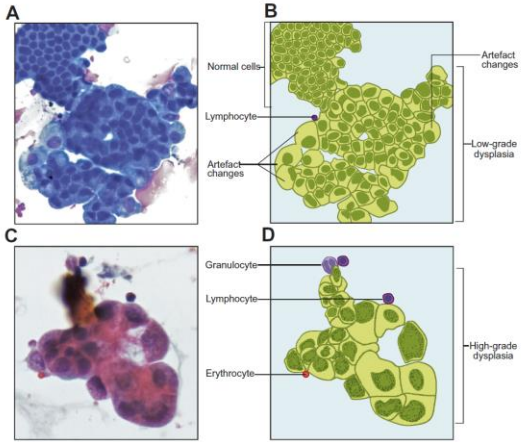
Surveillance for malignancy

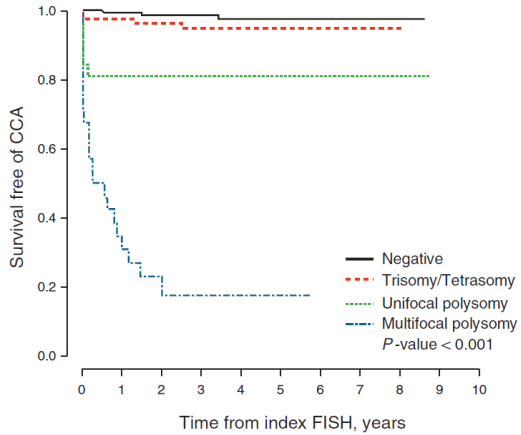




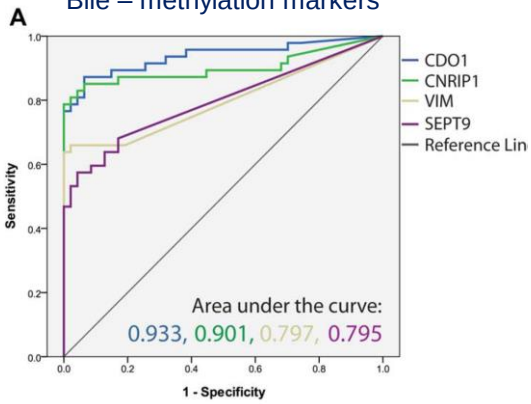
(Boonstra et al., 2013)

From morphology to molecular diagnoses

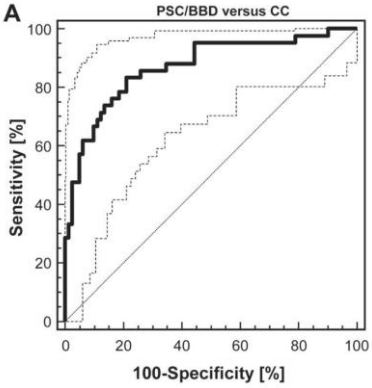




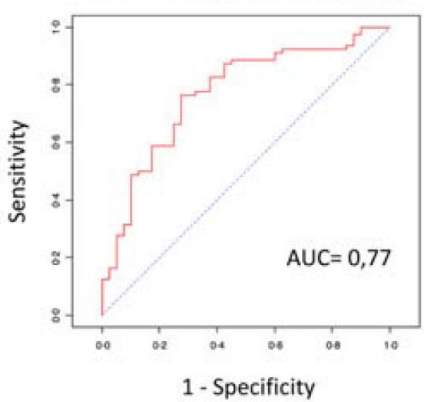
Bile – methylation markers



Urine – peptide/protein markers



Blood – microRNA markers



(Karlsen et al. 2017, Eaton et al. 2015, Andresen et al. 2015, Metzger et al. 2013, Bernuzzi et al. 2016)

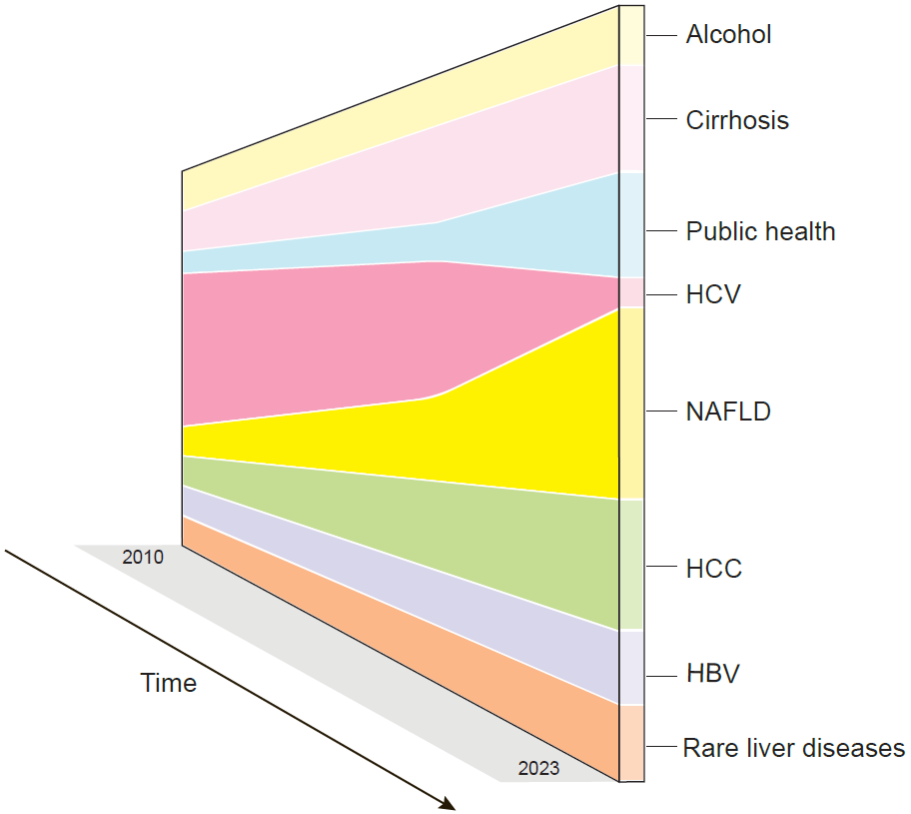
Digitial medicine and AI

EASL
The Home of Hepatology

Specialty	Images	Publication
Radiology/Neurology	CT head, acute neuro events	Titano, Nature Medicine, 2018
	CT head for brain hemorrhage	Arbabshirani, NPJ (Nature) Digital Medicine, 2018
	CT head for trauma	Chilamkurthy, Lancet 2018
	CXR for metastatic lung nodules	Gang Nam, Radiology 2018
	CXR for multiple findings	Singh, PLOS One, 2018
Pathology	Breast cancer	Bejnordi, JAMA, 2017
	Lung cancer (+ driver mutation)	Coudray, Nature Medicine 2018
	Brain tumors (+ methylation)	Capper, Nature, 2018
	Breast cancer metastases*	Steiner, Am J Surgical Pathology, 2018
	Breast cancer metastases	Liu, Arch Path Lab Med, 2018
Dermatology	Skin cancers	Esteva, Nature, 2017
	Melanoma	Haenssle, Annals of Oncology, 2018
	Skin lesions	Han, Journal of Investigative Dermatology
Ophthalmology	Diabetic retinopathy	Gulshan, JAMA, 2016
	Diabetic retinopathy*	Abramoff, NPJ (Nature) Digital Medicine, 2018
	Diabetic retinopathy*	Kanagasingam, JAMA Open 2018
	Congenital cataracts	Long, Nature Biomedical Engineering, 2017
	Retinal diseases (OCT)	De Fauw, Nature Medicine, 2018
	Macular degeneration	Burlina, JAMA Ophthalmology, 2018
	Retinopathy of Prematurity	Brown, JAMA Ophthalmology, 2018
	AMD and diabetic retinopathy	Kermany, Cell, 2018
Gastroenterology	Polyps at colonoscopy*	Mori et al, Annals Internal Medicine, 2018
Cardiology	Echocardiography	Madani, NPJ (Nature) Digital Medicine, 2018
	Echocardiography	Zhang, Circulation 2018

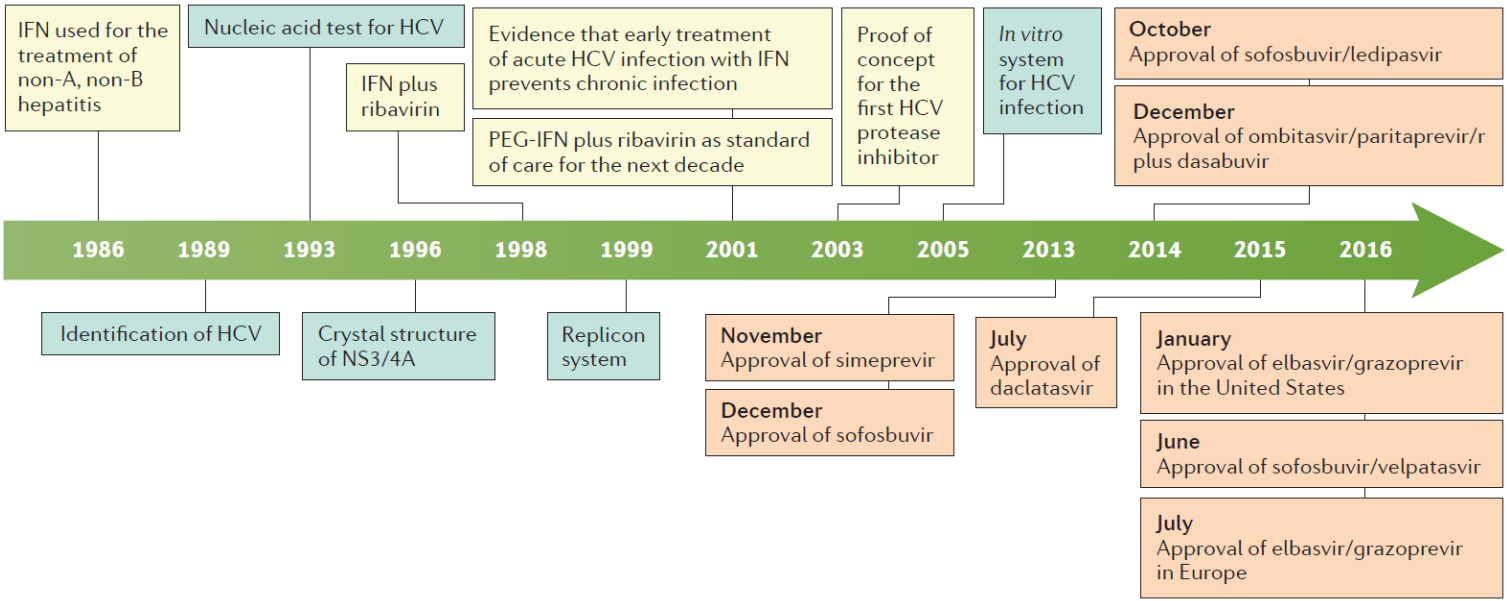
(Eric Topol, @erictopol)

A changing landscape of liver research



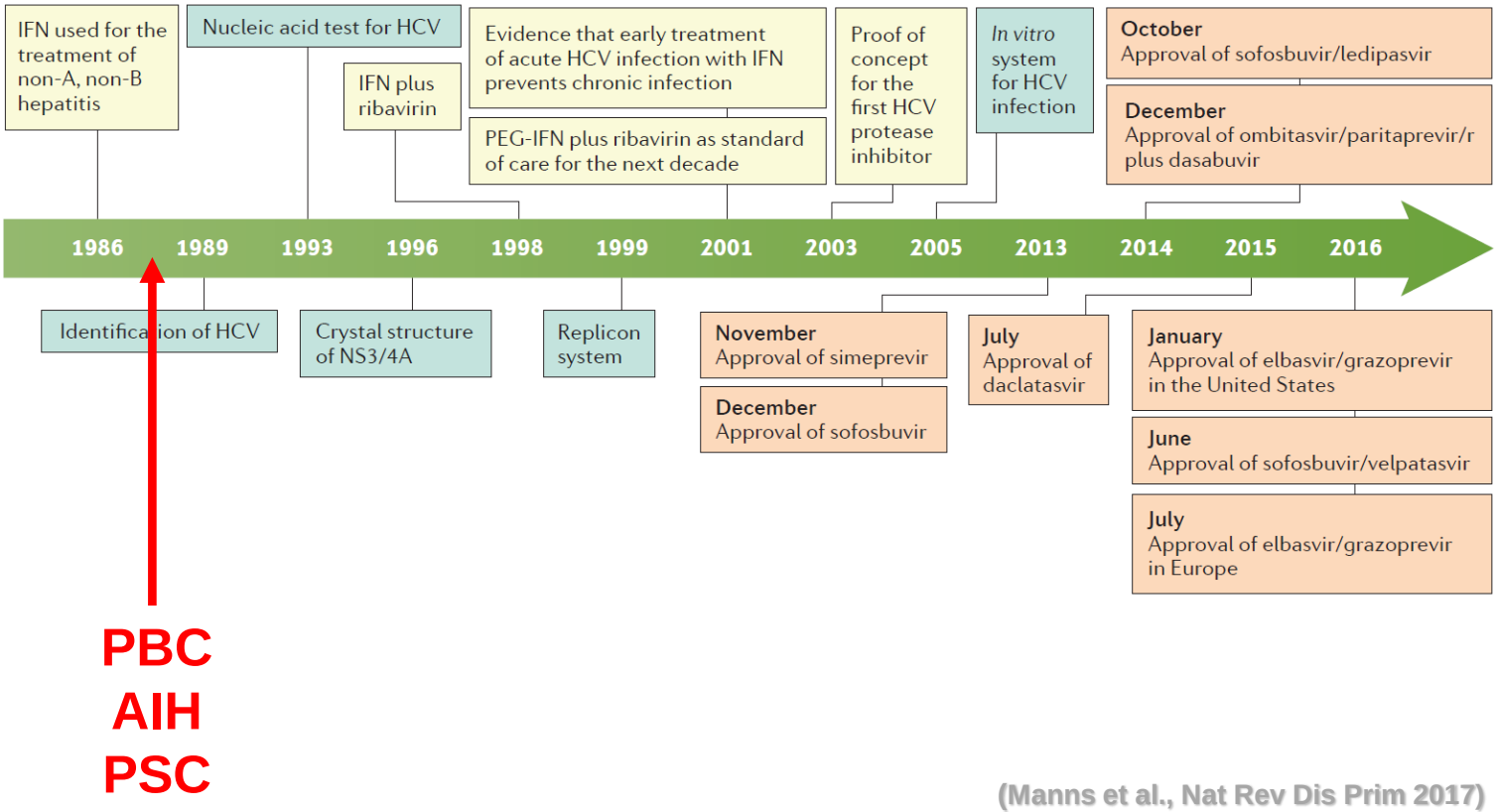
(Karlsen and Tacke, 2018)

A changing landscape of liver research



(Manns et al., Nat Rev Dis Prim 2017)

A changing landscape of liver research



PBC
AIH
PSC

(Manns et al., Nat Rev Dis Prim 2017)

Take home messages

- Treatment in PBC, AIH and PSC is still “antique”
- Second line therapies in PBC: bezafibrate vs. OCA
- Second line therapy in AIH: expert opinion recommendations only
- PSC signals from antibiotics and bile acid therapeutics
- Surveillance and biomarkers challenging, digital medicine and AI