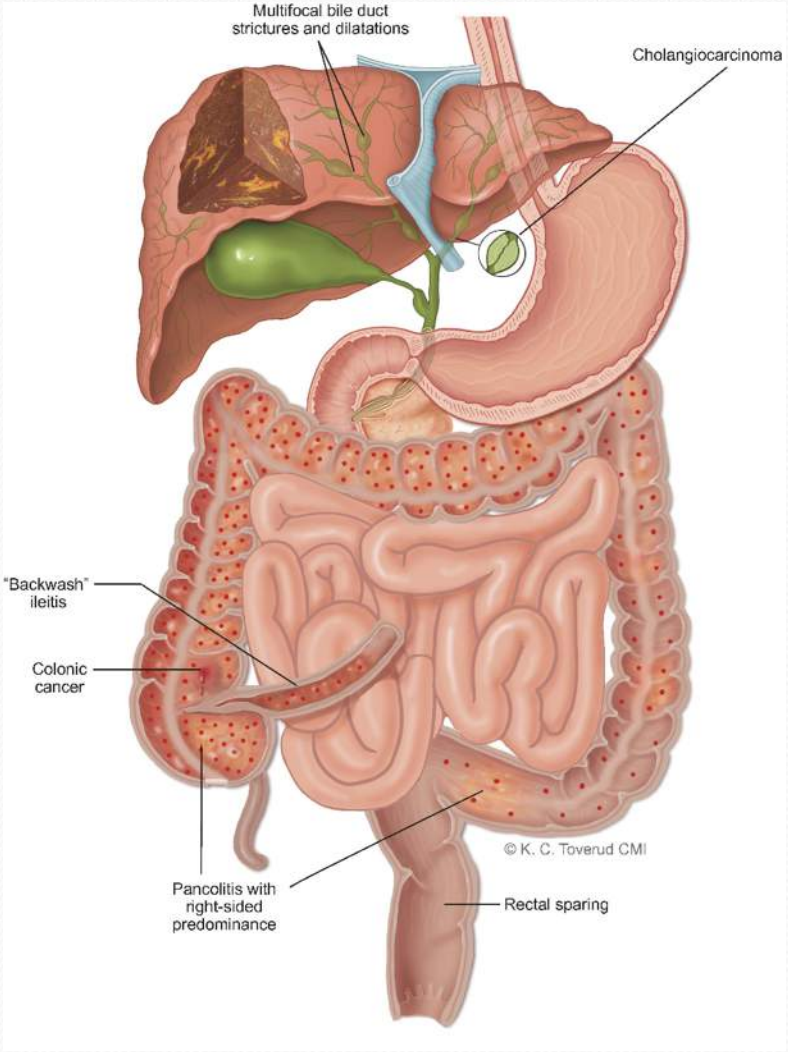
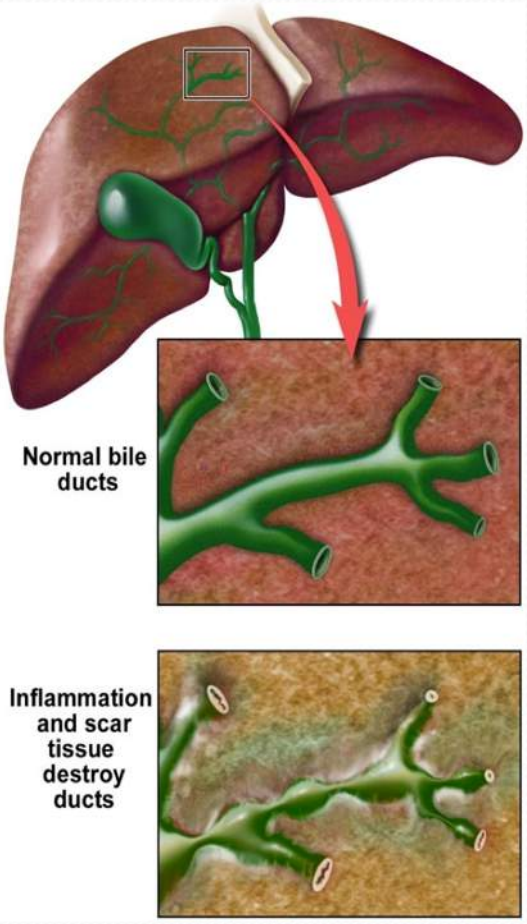
“Primary Sclerosing Cholangitis”

Dr Brijesh Srivastava
Consultant Hepatologist
UHW, Cardiff



Karlsen, T.H et al. Volume 67, Issue 6, December 2017, Pages 1298-1323

Primary Sclerosing Cholangitis



- Chronic cholestatic liver disorder characterised by inflammation & fibrosis of intra/extra hepatic bile ducts
- Leads to progressive bile duct obliteration, liver fibrosis and biliary cirrhosis
- Complex disease of unknown etiology
- Incidence ≈ 0.9-1.3/100,000/yr; Prevalence ≈ 8.5-14.2/100,000
- 60-80% have co-existing IBD; ≈ 25% have auto-immune disease
- 5th commonest indication for OLT
- Diagnosed on the basis of cholangiography (ERCP/PTC/MRCP) and/or histology

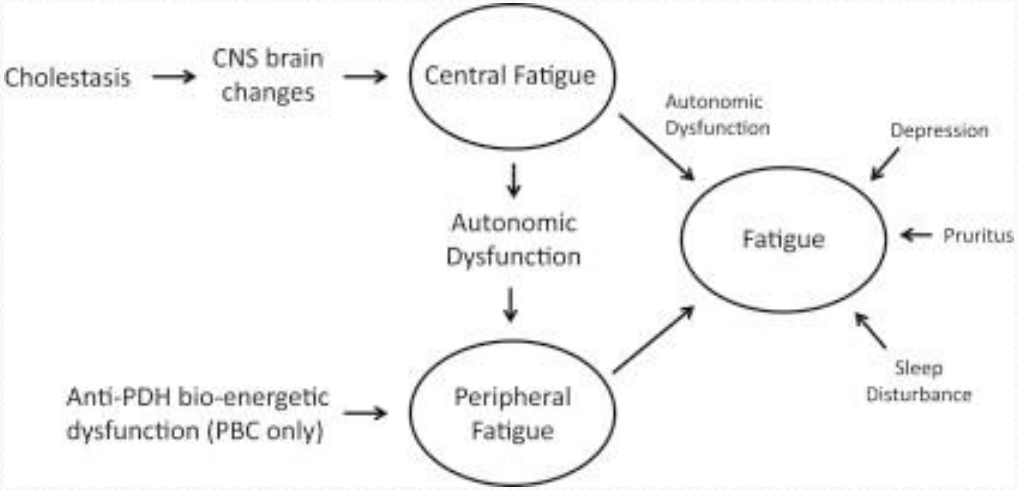
Diagnosis

- Early PSC can be difficult to diagnose
- High index of clinical suspicion
- Distinction with other phenotypes
  - Small-duct PSC
  - AIH overlap
  - IgG4 related sclerosing cholangitis

Presenting symptoms

- 25% asymptomatic
- Abdominal pain
- **Itch**
- **Fatigue**
- Jaundice
- Recurrent bouts of cholangitis

Fatigue



Jopson L et al. Clin Liver Dis. 2016 Feb;20(1):131-42

UK-PSC consortium

- Recruit homogeneous cohort of PSC patients
- Phenotypic characterisation
- Attempt to define:
  - genetic predisposition/risk in PSC
  - most plausible biological pathways in pathogenesis
- Develop a national database to enable present and future epidemiological, genetic and immunological studies

Phenotypic characteristics of the UK-PSC cohort

Recruitment

- Total no. of patients recruited = > **2000**
  (~ 50% from transplant centres)

- 1291 patients completed detailed questionnaire

- Liver transplant recipients = 320
  - 27 (8.5%) patients underwent 2nd transplantation
  - Further 3 patients received 3rd transplant

Demographics

- Median age at recruitment (entire cohort) = 58 years

- Age at diagnosis of PSC (data available for 600 patients):

  - median age at diagnosis of PSC = **46 years** (16–86 yrs)

- 330/600 had IBD:

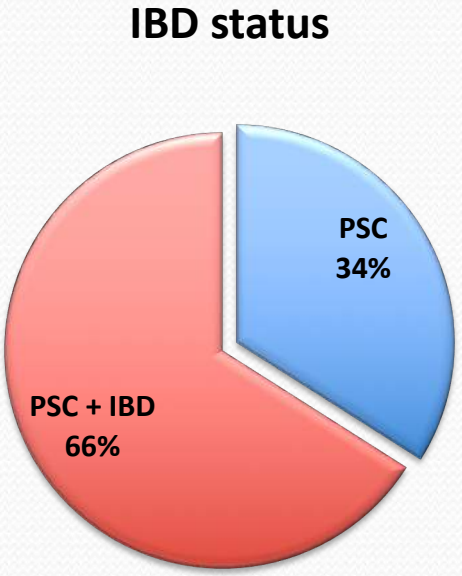
  - median age at diagnosis of IBD = 27 years (6–70 yrs)

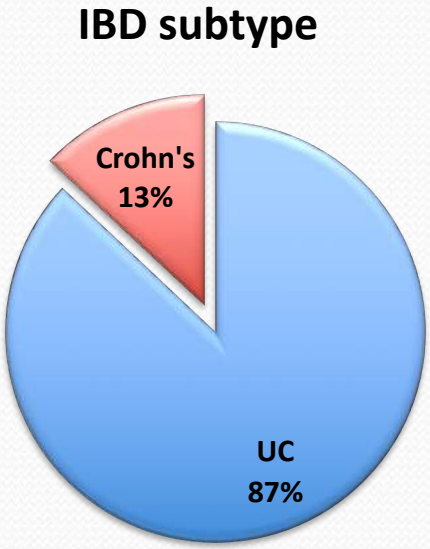
- Gender: Males = 812 (63%); Females = 479 (37%)

  M:F = 1.7:1

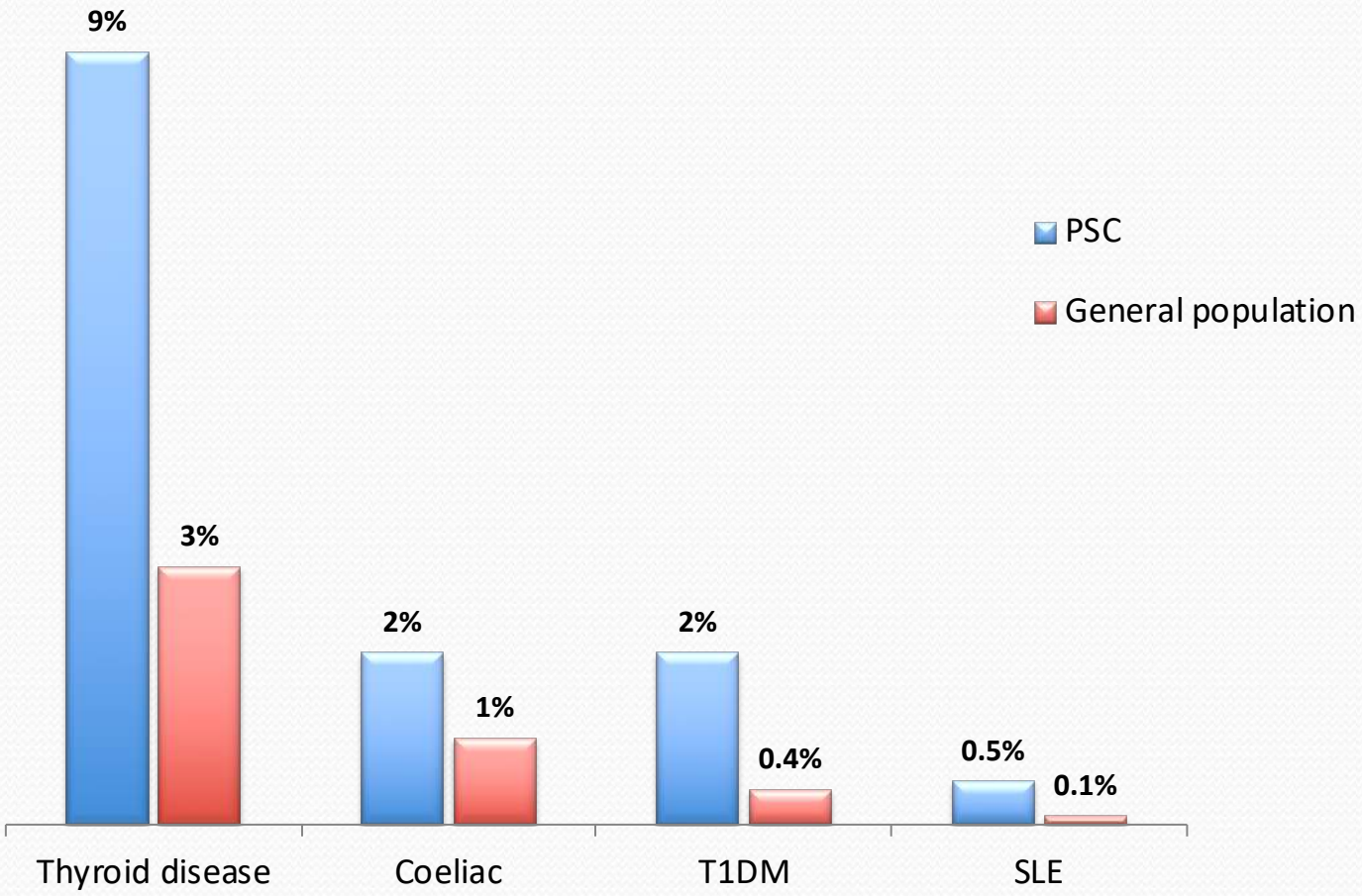
Inflammatory bowel disease

- 847/1291 patients had IBD
- UC = 730 (87%)
- Crohn's = 112 (13%)





Autoimmune diseases



Summary

- Largest reported cohort of PSC patients
- PSC more prevalent in young, non-smoking males
- ↑ prevalence of IBD and immune-mediated diseases
- Is PSC an immune mediated disease occurring in genetically susceptible individuals?
- Does PSC share any pathological pathways with other immune-mediated diseases?

Immune and Genetic risk in PSC

PSC vs Autoimmune diseases

Characteristic	Classical AID	Immune-mediated inflammatory d/s (UC, Psoriasis)	PSC
Age	Children & Adults	Children & Adults	Children & Adults
Sex	Female predominance	No sex predilection	Male predominance
Autoantigens	Yes	No	No
Autoantibodies	Yes (pathogenic)	Yes (markers)	Yes (probably markers)
HLA association	Yes	Yes	Yes
Response to immunosuppression	Usually good	Often good	Good in children Poor in adults

Chapman et al. Pathogenesis of PSC. WJG 2008 June 7; 14(21): 3350-3359

Proposed pathogenetic mechanisms

- Immunogenetics:
  - MHC genes/HLA association
  - **Non-MHC genetic association**

- Aberrant lymphocyte homing & auto-reactivity

- The “leaky gut” hypothesis

GWAS

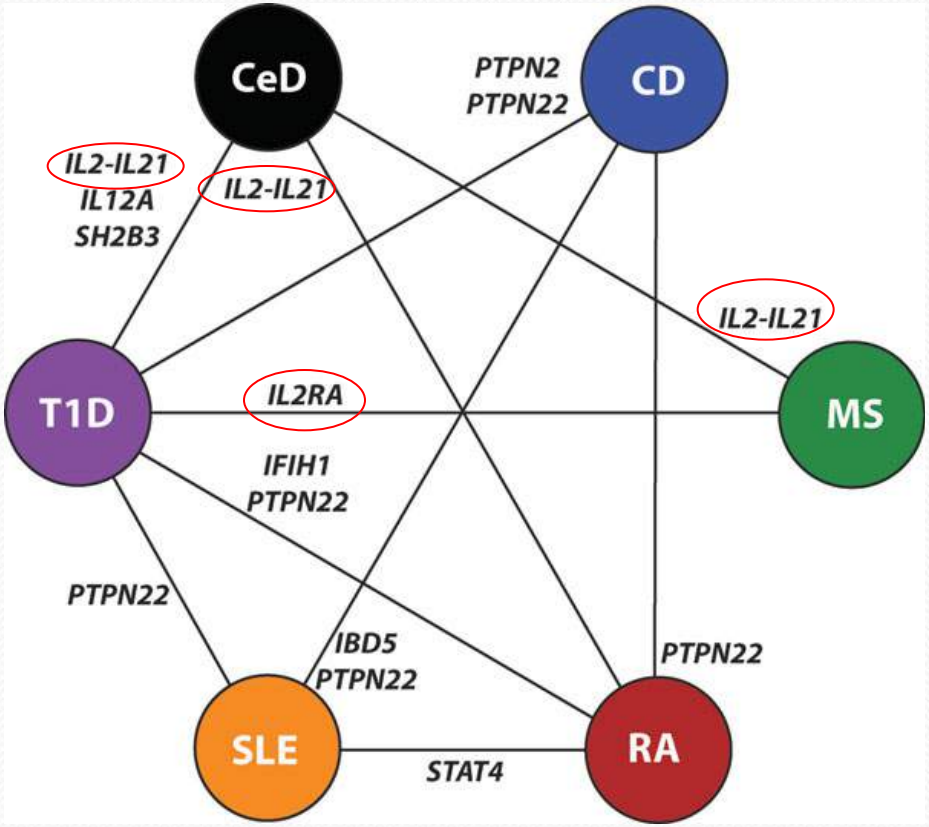
- Non-hypothesis driven
- Case-control association study comparing SNP's between patients vs controls

- 0.5 – 1 million SNPs are typically genotyped (allows coverage of most of the common variants across the genome) in discovery panel
- Most associated SNPs ($p < 5 \times 10^{-5}$) genotyped in an independent panel for replication/verification

- allows identification of genetic regions probably associated with disease

Table 8.3. Timeline of all non-HLA susceptibility loci associated with PSC.

Year	Chr	Lead SNP	Candidate gene	UK PSC data included	Ref
2011	2q13	rs6720394	*BCL2L11*	No	(145)
	3p21	rs3197999	*MST1*	No	
2012	10p15	rs4147359	*IL2RA*	**Yes**	(208)
2012	1p36	rs3748816	*MMEL1, TNFRSF14*	No	(146)
2013	2q33	rs7426056	*CD28, CTLA4*	**Yes**	(202)
	4q27	rs13140464	*IL2, IL21*		
	6q15	rs56258221	*BACH2*		
	11q23	rs7937682	*SIK2*		
	12q13	rs11168249	*HDAC7*		
	12q24	rs3184504	*SH2B3, ATXN2*		
	18q22	rs1788097	*CD226*		
	19q13	rs60652743	*FUT2, PRKD2, STRN4*		
	21q22	rs2836883	*PSMG1*		
2013	2q37	rs3749171	*GPR35*	No	(209)
	18q21	rs1452787	*TCF4*		
2016	2q36	rs7556897	*CCL20*	No	(210)
	4q24	rs3774937	*NFKB1*		
	12q23	rs12369214	*RFX4, RIC8B*		
2017	3p13	rs80060485	*FOXP1*	**Yes**	(203)
	11q13	rs663743	*CCDC88B*		
	16p13	Rs725613	*CLEC16A, SOCS1*		
	21q22	rs1893592	*UBASH3A*		



Ekta Rai, smim, Feb 2011, Genetic predisposition to autoimmunity.

Genetic risk Summary

- These SNPs probably are - candidate drivers for shared genetic architecture between diseases

- Common genetic/biological mechanisms may underlie observed clustering of AI-diseases in individuals or family

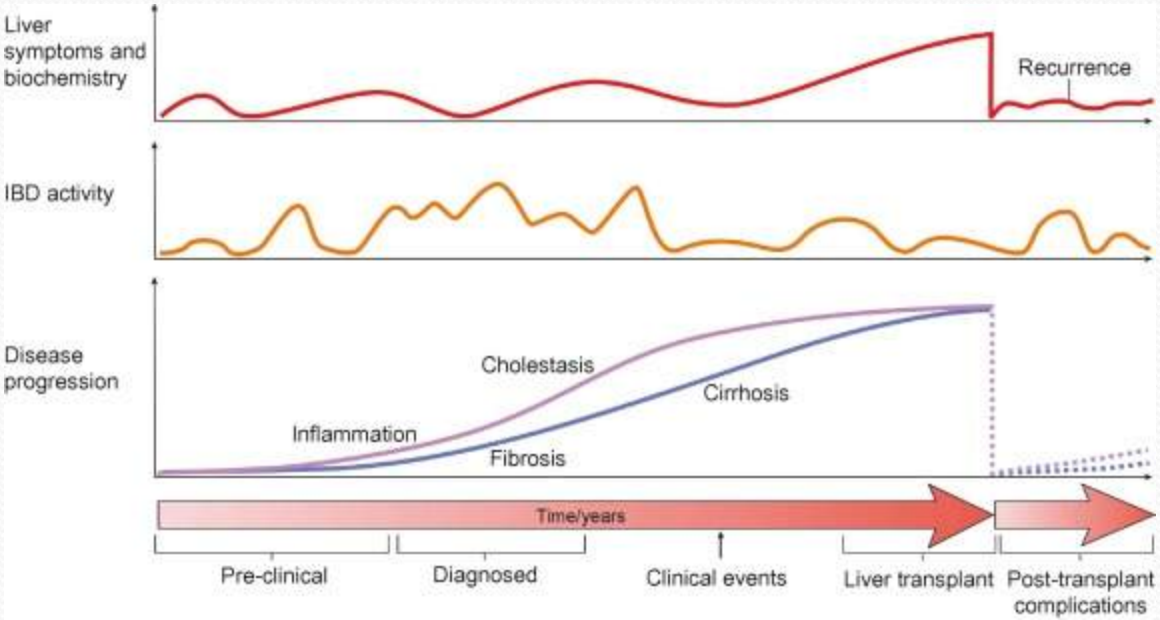
- Grouping variants by the diseases they influence can provide:
  - Predictive models of disease risk
  - mechanistic insights into disease development

Risk stratification

Natural history

- Variable progression (**not everyone progresses**)
- Complications of PSC (cholangitis, jaundice, malignancy ~ 10-15%)
- Progressive biliary cirrhosis (~ 20 - 30%)
- Complications of cirrhosis

Natural history



UK-PSC Risk Score

- Short-term and long-term risk prediction
- Significance of ALP remains unclear (variable levels)
- Score more relevant for research trials
- Extent of disease is more important (intra or extra-hepatic)

Treatment

- Several drugs have been studied
- None alter disease progression

Treatment

- Drugs evaluated in treatment of PSC

Immunosuppressive	Anti-fibrotic	Anti-TNF
Steroids	Colchicine	Infilximab
Budesonide	Penicillamine	Etanercept
Tacrolimus/Cyclosporine	Pirfenidone	
Azathioprine/MMF		
Methotrexate		

- No impact on disease progression or prognosis
- AIH overlap/IgG4 sub-group improve with steroids

Role of UDCA in PSC

- Meta-analysis (8 RCTs) (1, 2):
  - 567 pts; 5 x standard dose; 3 x high dose
  - Improvement in biochemical profile
  - No improved survival with standard or high-dose
  - Median F/U = 3 months – 6 yrs
  - Small no. of patients (n = 567)

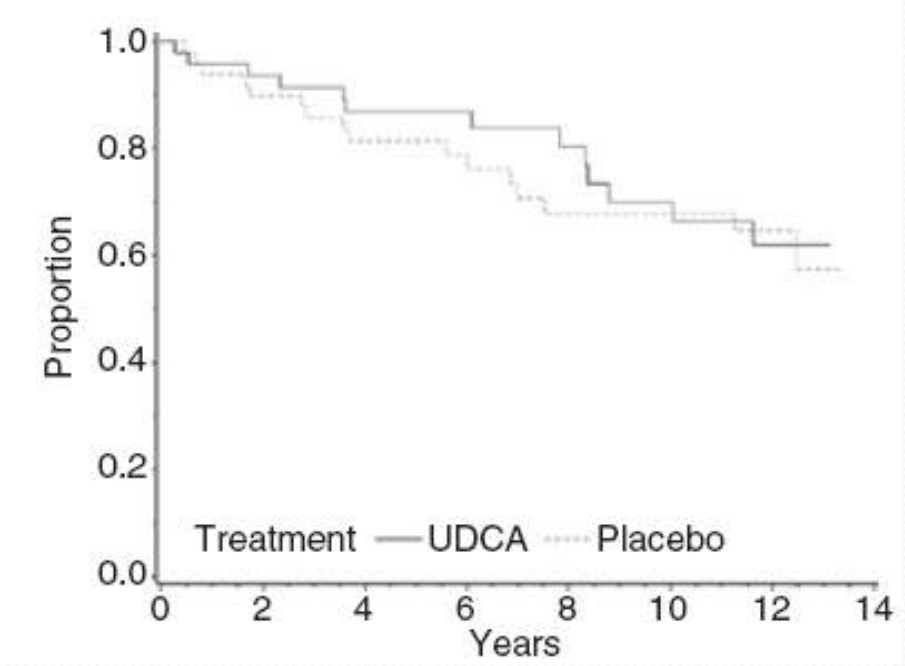
- Not enough evidence to support/refute use of UDCA

1) *Triantos et al, Aliment Pharmacol Ther 2011.*
2) *Poropat G et al, Cochrane Database Syst Rev, 2011.*

UDCA in PSC/IBD

- Chemopreventive effect of UDCA on risk of CRC/dysplasia has been suggested
- Mainly limited by sample size (n = 50 – 100)

- *5 yr RCT of UDCA vs placebo
- 98 PSC-IBD cases
- Median f/u – 12 yrs
- No protective effect of UDCA seen



*Lindstrom L et al, Aliment Pharmacol Ther 2012.

	Rx of PSC	Chemoprevention for CRC in PSC/UC
EASL (2009)	Limited data base does not yet allow a specific recommendation for UDCA use	- Suggestive but limited evidence - Consider in high risk groups: strong F/H of CRC, previous CRC or long-standing colitis
AASLD (2010)	Recommend against the use of UDCA	Recommend against the use of UDCA
BSG (2018)	No role for UDCA	No role for UDCA

Management of PSC

- General lifestyle measures
  - healthy diet/exercise/physical activity
  - alcohol (< 14units/week)
  - medications (antibiotics/analgesics)

- Itch
  - cholestyramine (1st line)
  - Rifampicin, Naltrexone (2nd line)

- Fatigue
  - no licensed treatment

Out-patient monitoring

- 6 – 12 monthly blood tests
- Annual Ultrasound scan (gall bladder polyps)
- Annual MRI scan (if involvement of large bile ducts)
- Screen for Oesteopenia/Vit D deficiency (~ 15%)
- Annual Colonoscopy (for PSC-IBD); Joint PSC-IBD clinic

Research

Table 1 Currently registered drug trials (ClinicalTrials.gov) in primary sclerosing cholangitis (PSC) listed by suggested modes of action

Nuclear and membrane receptor ligand-based therapies			
Obeticholic acid	FXR agonist	NCT02177136 Phase 2	AESOP, open-label phase ongoing
GS-9674	Selective, non-steroidal FXR agonist	NCT02943460 Phase 2	Significant reduction of AP with 100mg at 12 weeks
FGF-19 signalling pathway analogues			
NGM282	Supposedly non-tumorigenic, engineered variant of the human hormone FGF-19	NCT02704364 Phase 2	Primary endpoint (statistically significant change in AP) not met according to a press release
PPAR agonists			
Fenofibrate	PPAR-α agonist	NCT01142323 Phase 2	Open label, significant reduction in AP and ALT; no significant change in Mayo PSC risk score
All-trans retinoic acid (ATRA)	Low-dose all-trans retinoic acid	NCT01456468 Phase 1 NCT03359174 Phase 2	Primary endpoint (statistically significant reduction in AP) not met in phase 1 study (completed), phase 2 ongoing
Bile acids			
*nor*Ursodeoxycholic acid (*nor*UDCA)	HCO_3^--rich choleresis-inducing bile acid derivative	Phase 3	
Cytokine/chemokine mediator targeting therapies			
Cenicriviroc	CCR2/CCR5 antagonist	NCT02653625 Phase 2	PERSEUS, completed December 2017
Vedolizumab	Anti-α4β7 integrin antibody	NCT03035058 Phase 3	withdrawn in early 2018
Timolumab (BTT1023)	Anti-VAP-1 antibody	NCT02239211 Phase 2	BUTEO
Antifibrotic therapy			
Simtuzumab	LOXL2 inhibition	NCT01672853 Phase 2b	Primary endpoint (significant change in hepatic collagen content) not met
Modulation of the gut microbiome			
Vancomycin	Antibiotic	NCT02605213 NCT02464020 NCT02137668 NCT01322386 NCT01802073 NCT01085760	
Rifaximin	Antibiotic	NCT01695174 (published)	Open-label pilot study, no significant improvements in serum AP, bilirubin, GGT, or Mayo PSC risk score
Minocycline	Antibiotic	NCT00630942	Open-label pilot study
Metronidazol	Antibiotic	NCT03069976	Peadiatric
Faecal microbiota transplantation		NCT02424175 Phase 1/2	

Wales PSC database

- Identify all PSC cases under follow-up in Wales
- Collect clinical & sub-group phenotypic data
- Collaborative studies with UK-PSC cohort and drug trials locally (POLARISE trial)
- Standardise care and reduce variations in practice

Acknowledgements

- **All PSC patients (UK-PSC cohort)**
- Principal Investigators & CLRN research nurses
- Genotyping laboratory in Kiel, Germany
- PSC Support UK
- Norwegian PSC Research centre