Ursodeoxycholic acid- an intervention worth pursuing

PSC Partners 2011

Gideon Hirschfield

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Conflict of interest statement

Company Name	Relationship
Intercept Pharma	Consultant, Investigator
Axcan Pharma	Speaker, Consultant
Centocor	Advisory board, Consultant
BMS	Investigator
Boehringer Ingelheim	Investigator
Tibotec	Investigator
Sanofi-Aventis	Advisory board
Merck	Speaker, Research support
Roche	Speaker

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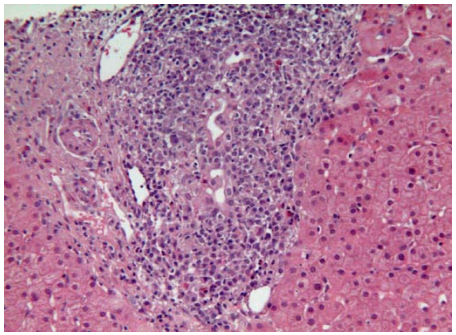
Over past 24 months

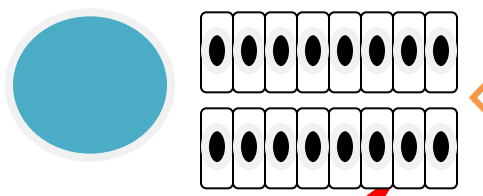
“Autoimmune” liver disease

UDCA ✔



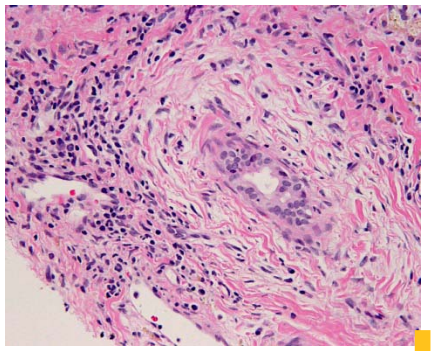
Granulomatous lymphocytic cholangitis

Central vein *Hepatocytes* *Portal triad*



PBC

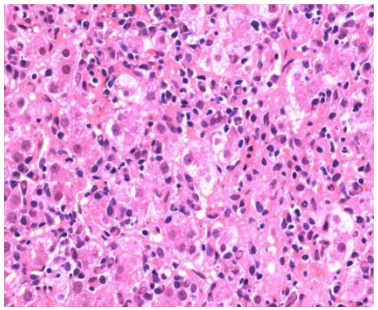
Small duct SC



Periductal “onionskin’ fibrosis

UDCA ✖

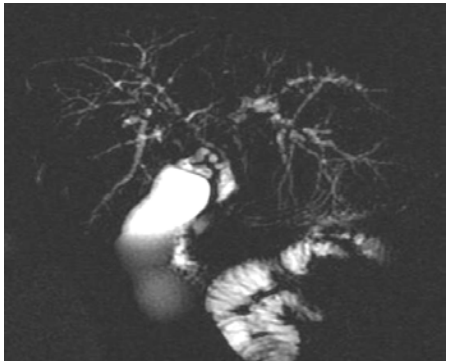
AIH



Lympho-plasmacytic infiltrate

UDCA ?

Large duct SC



Biliary strictures and dilatation

Duodenum

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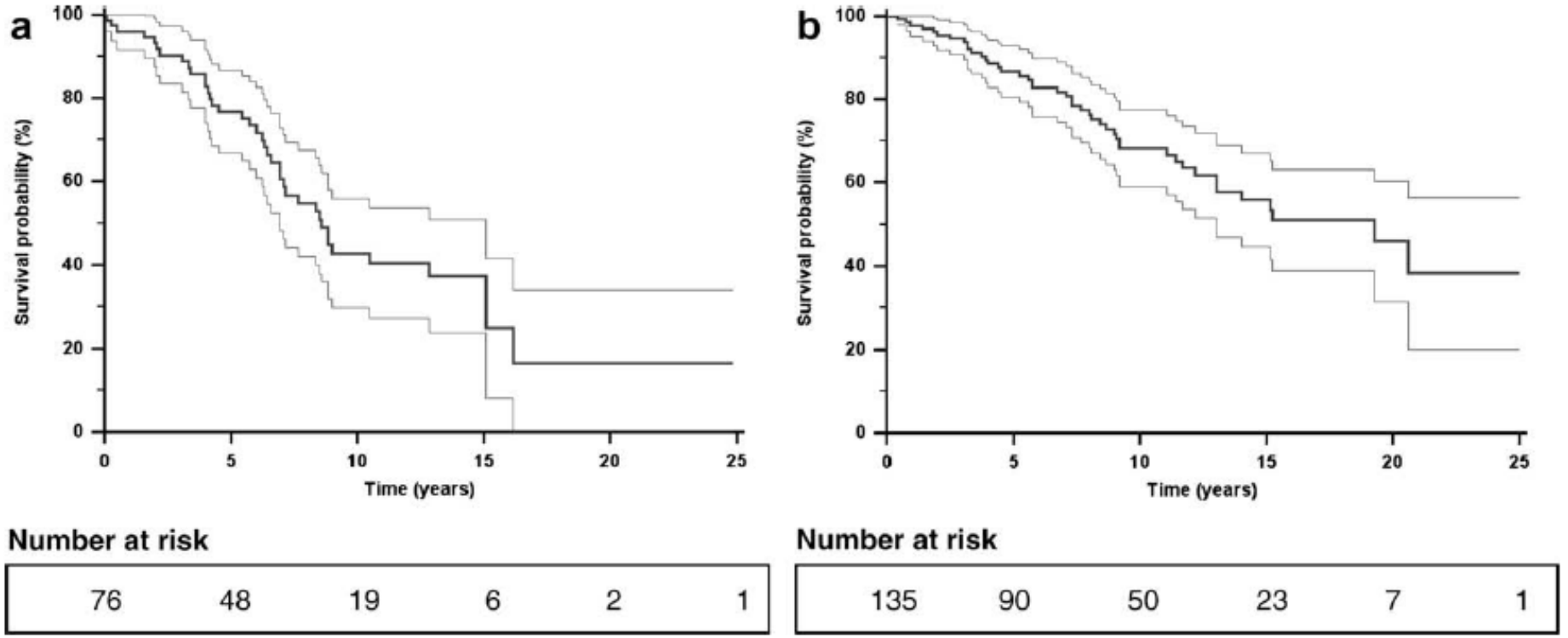
BMJ 2009 Sep 8;339:b3305

A slow disease that we are determined to change

Symptomatic at presentation

Asymptomatic at presentation



Transplantation-free survival (+95% CI) for 211 patients with PSC

LONG NATURAL HISTORY- MAJOR ISSUE FOR TRIALS

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Journal of Hepatology (2009) 158–164

PSC in 1980- LATE PRESENTATION

Table 2 *Laboratory investigations*

	No.	*Normal range*	*Primary sclerosing cholangitis*		
			Mean	*Range*	*% Abnormal*
Bilirubin (μmol/l)	29	0–17	84	9–459	83
Alkaline phosphatase (KAU/l)	29	3–13	69	6–172	97
Amino transferase (IU/l)	29	4–15	62	19–226	97
Albumin (g/l)	28	35–50	39	25–47	29
IgM (g/l)	20	0·7–2·8	3·28	0·8–11·7	45

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Chapman et al. Gut 1980

2011 – EARLY PRESENTATION: TIME TO INTERVENE

Factor	Category	Sub Category	All (N = 199)	Men (n = 142)	Women (n = 57)
Age in years, median (range)			38.5 (18.0-76.8)	38.7 (18.2-73.9)	37.6 (18.0-76.8)
Inflammatory bowel disease (IBD)	Yes	Any IBD	152 (76.4%)	117 (82.4%)	35 (61.4%)
		Ulcerative colitis	129 (64.8%)	104 (73.2%)	25 (43.9%)
		Crohn disease	17 (8.5%)	9 (6.3%)	8 (14.0%)
		Indeterminate colitis	5 (2.5%)	3 (2.1%)	2 (3.5 %)
		Microscopic colitis	1 (0.5%)	1 (0.7%)	0 (0%)
	No		47 (23.6%)	25 (17.6%)	22 (38.6%)
Extension of biliary involvement	Only intrahepatic		61 (30.7%)	47 (33.1%)	14 (24.6%)
	Extrahepatic and/or intrahepatic		115 (57.8%)	81 (57.0%)	34 (59.6%)
	Small duct disease		20 (10.1%)	12 (8.5%)	8 (14.0%)
	Unknown		3 (1.5%)	2 (1.4%)	1 (1.8%)
Symptoms at diagnosis	Yes	Any symptom	93 (46.7%)	62 (43.7%)	31 (54.4%)
		Jaundice	48 (24.1%)	32 (22.5%)	16 (28.1%)
		Cholangitis	19 (9.5%)	13 (9.2%)	6 (10.5%)
		Itching	20 (10.1%)	14 (9.9%)	6 (10.5%)
		Abdominal pain	50 (25.1%)	34 (23.9%)	16 (28.1%)
		Other	66 (33.2%)	48 (33.8%)	18 (31.6%)
	No		106 (53.3%)	80 (56.3%)	26 (45.6%)

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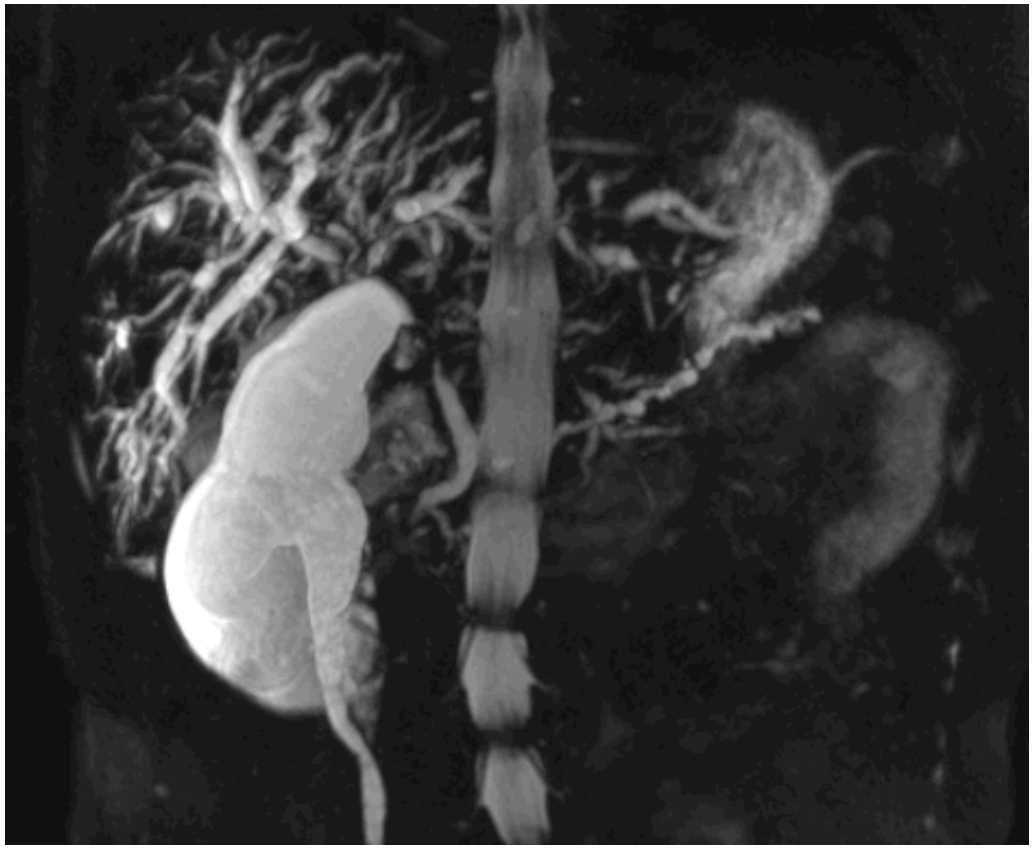
Secondary sclerosing cholangitis



The variety of secondary causes mimicking histologic and radiological features of PSC (including **autoimmunity, ischemia, infection and toxins**) suggests commonality in final pathways associated with biliary injury

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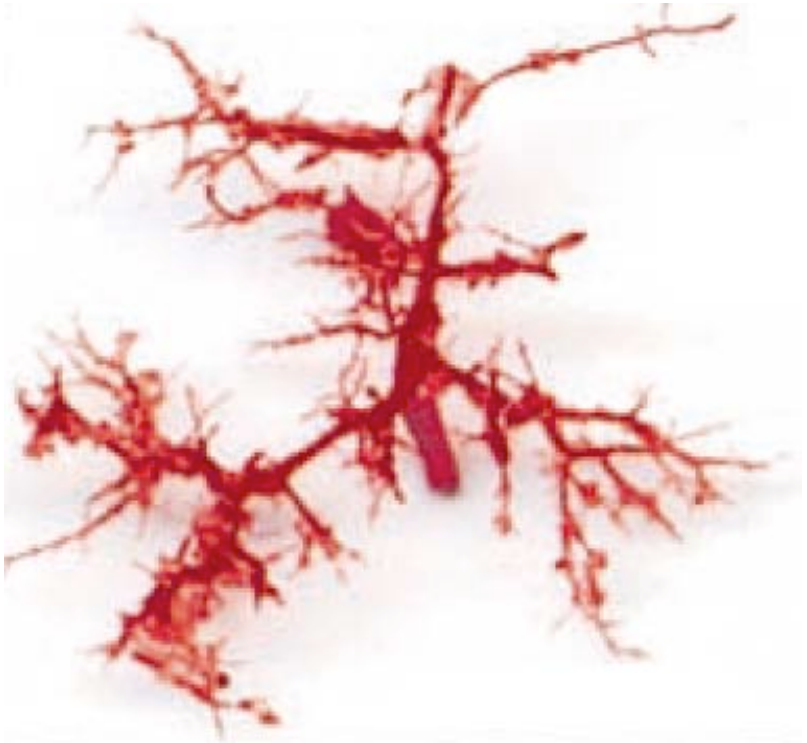
Mdr2 deficient *mice develop* cholangiopathy



BEST ANIMAL
MODEL OF DISEASE
IS FROM BILE ACID TOXICITY

Gastroenterology 2002;123:1238–1251

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UDCA – an ancient bear treatment

- **UDCA had been isolated in Japan in 1927 from dried bile of the black bear (“Yutan”) which was used in traditional Chinese and Japanese medicine as a remedy for liver and gastrointestinal disorders for centuries.**

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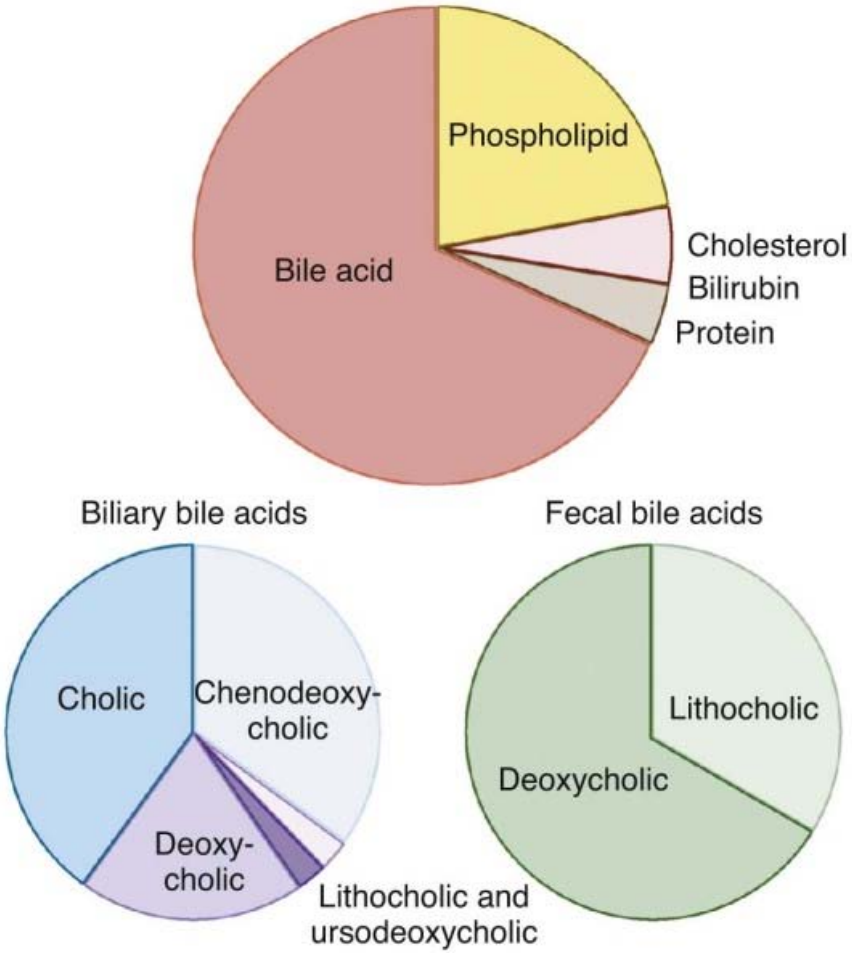
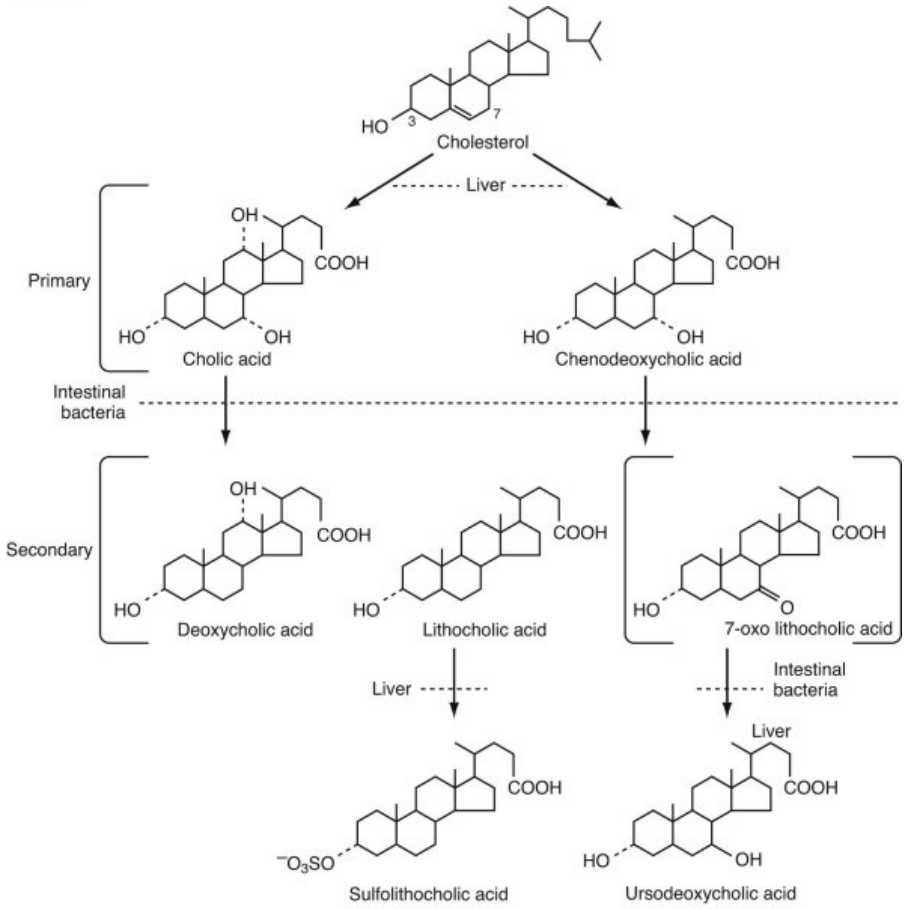
Bile constituents



Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 9th ed.

Major primary and secondary bile acids and their sites of synthesis and metabolism



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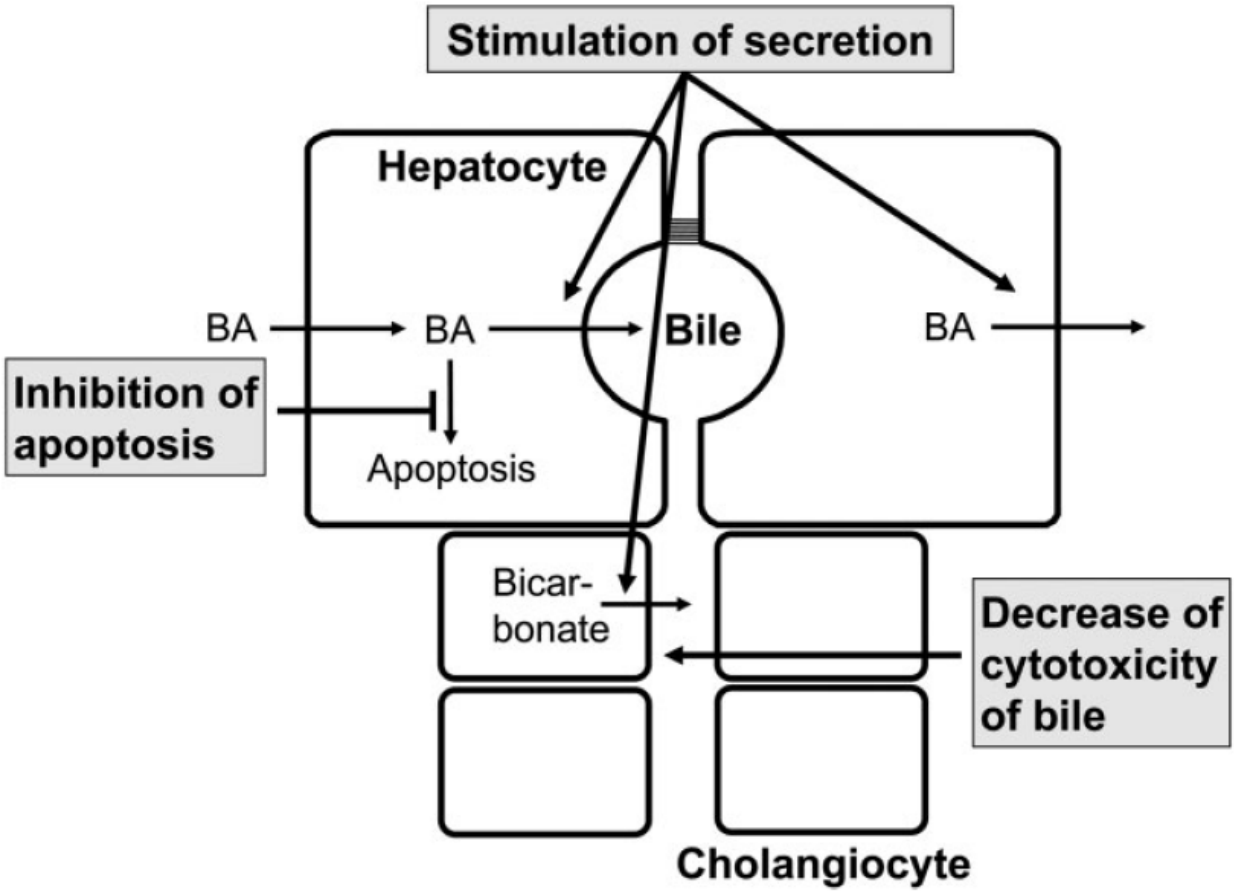
Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 9th ed.

Major targets of ursodeoxycholic acid therapy in cholestatic liver diseases- a good liver tonic



HEPATOLOGY, Vol. 51, No. 4, 2010

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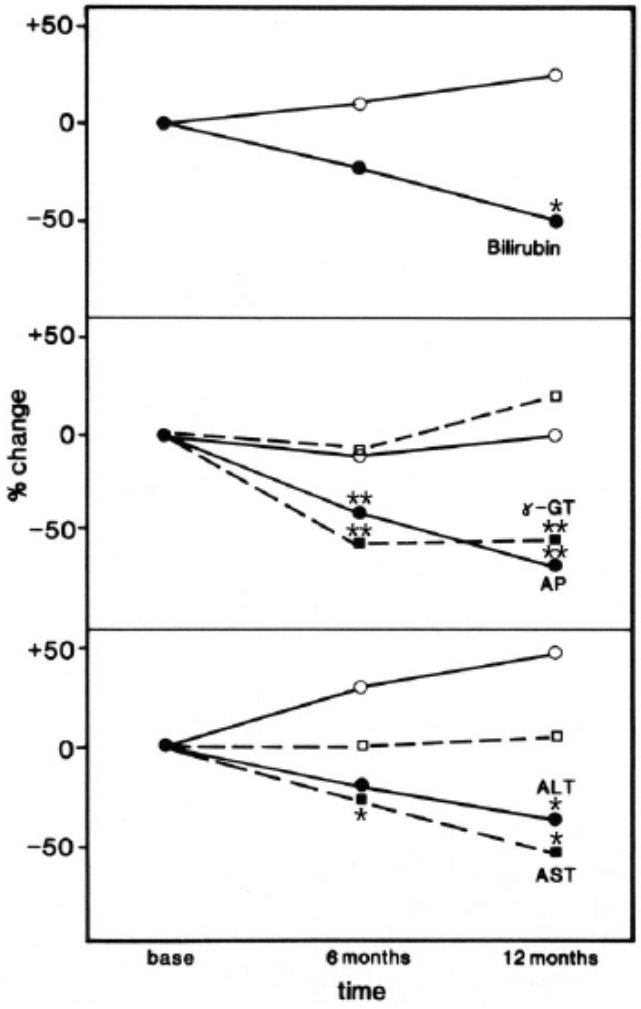
Beuers U et al.
Ursodeoxycholic acid for treatment of primary sclerosing cholangitis: a placebo-controlled trial.



13-15 mg/kg/day of UDCA

HEPATOLOGY 1992;16:707-714.

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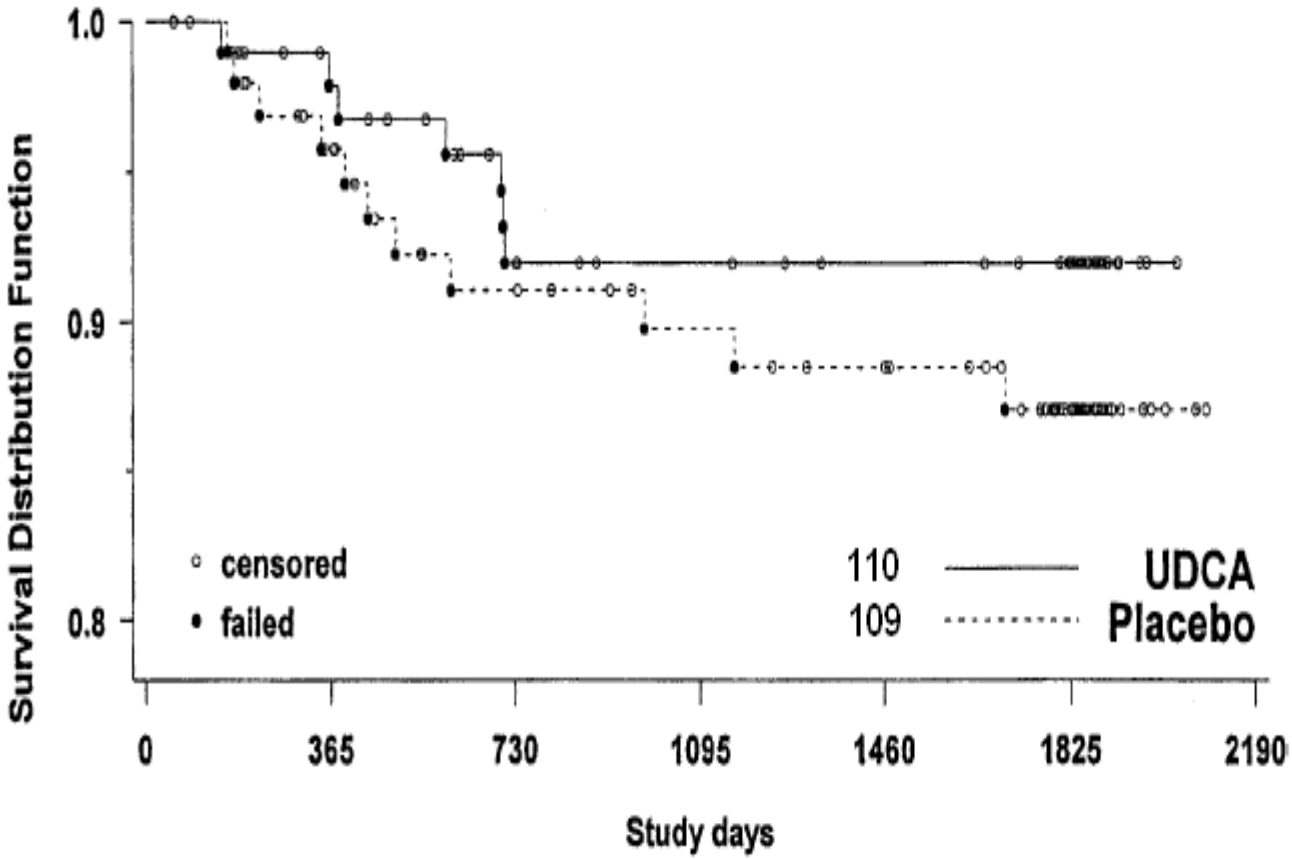
RCT: UDCA (23mg/kg/d) vs Placebo



Death/Tx - 7 (7.2) UDCA
- 11 (10.9) placebo

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Symptoms and biochemistry

Table 3 Effect on symptoms and biochemical values of ursodeoxycholic acid treatment in the trials included in meta-analysis

Study, year	Fatigue	Pruritus	AST	ALT	γ-GT	ALP	Bilirubin	Albumin	Mayo score
Beuers *et al.*, 1992[6]	–	–	++	++	++	++	++	NR	+
Lo *et al.*, 1992[18]	–	–	+	NR	+	+	+	NR	NR
Stiehl *et al.*, 1994[7]	–	–	NR	++	++	++	+	–	–
De Maria *et al.*, 1996[19]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bansi *et al.*, 1996[20]	–	–	+	NR	++	++	+	–	NR
Lindor, 1997[9]	NR	NR	++	NR	NR	++	++	–	NR
Mitchell *et al.*, 2001[8]	–	–	+	NR	++	++	+	–	NR
Olsson *et al.*, 2005[21]	NR	–	NR	+	NR	+	+	–	NR

–, No significant change; +, improvement trend comparing UDCA with placebo or no treatment; ++, significant improvement. γ-GT, gamma glutamyl transpeptidase; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; NR, not reported.

Hepatology Research 2009; **39**: 865–873

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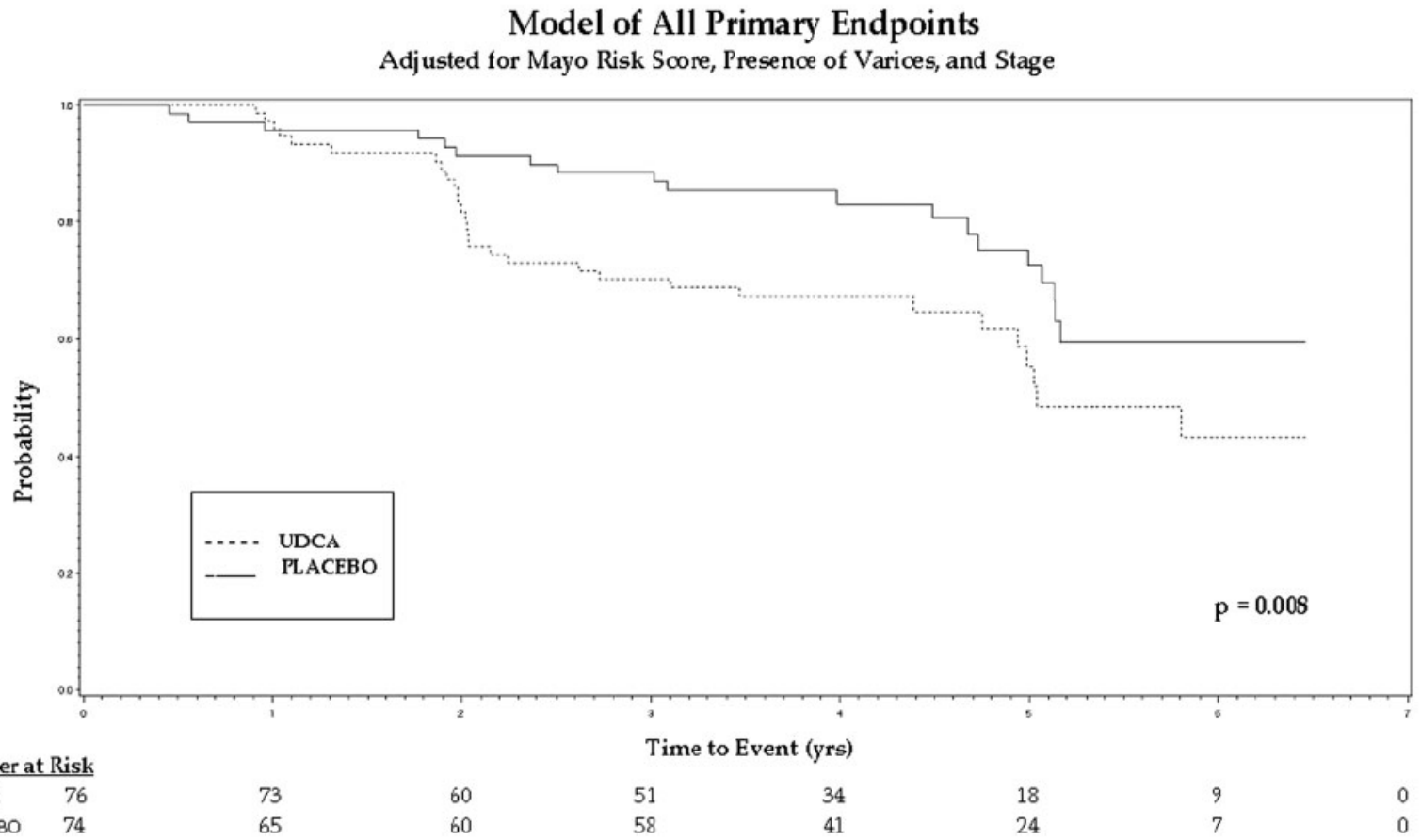
High dose UDCA vs Placebo



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

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HEPATOLOGY, Vol. 50, No. 3, 2009

Still relatively few patients studied

Table 1. Selected Trials of Ursodeoxycholic Acid for Treatment of Primary Sclerosing Cholangitis

First Author	Year Published	No. of Patients	Dose of UDCA/Day	Type of Trial	Trial Period (Months)	LFTS Improved?	Symptoms Improved?	Liver Histology Improved?
Beuers[6]	1992	6	13-15 mg/kg	Double-blind, placebo-controlled	12	Y	N	Y
Stiehl[7]	1994	20	750 mg	Double-blind, placebo-controlled	12-48	Y	N	Y
Lindor[8]	1997	105	13-15 mg/kg	Double-blind, placebo-controlled	34	Y	N	N
Mitchell[10]	2001	26	20-25 mg/kg	Double-blind, placebo-controlled	24	Y	N	Y
Harnois[13]	2001	30	25-30 mg/kg	Open label	12	Y	Not done	Not done
Okolicsanyi[23]	2002	86	8-13 mg/kg	Open-label, placebo-controlled	120	Y	Y	N
Olsson[11]	2004	110	17-23 mg/kg	Double-blind, placebo-controlled	60	Y	N	Not done
Lindor[9]	2009	150	25-30 mg/kg	Double-blind, placebo-controlled	60	Y	N	N

HEPATOLOGY, Vol. 50, No. 3, 2009

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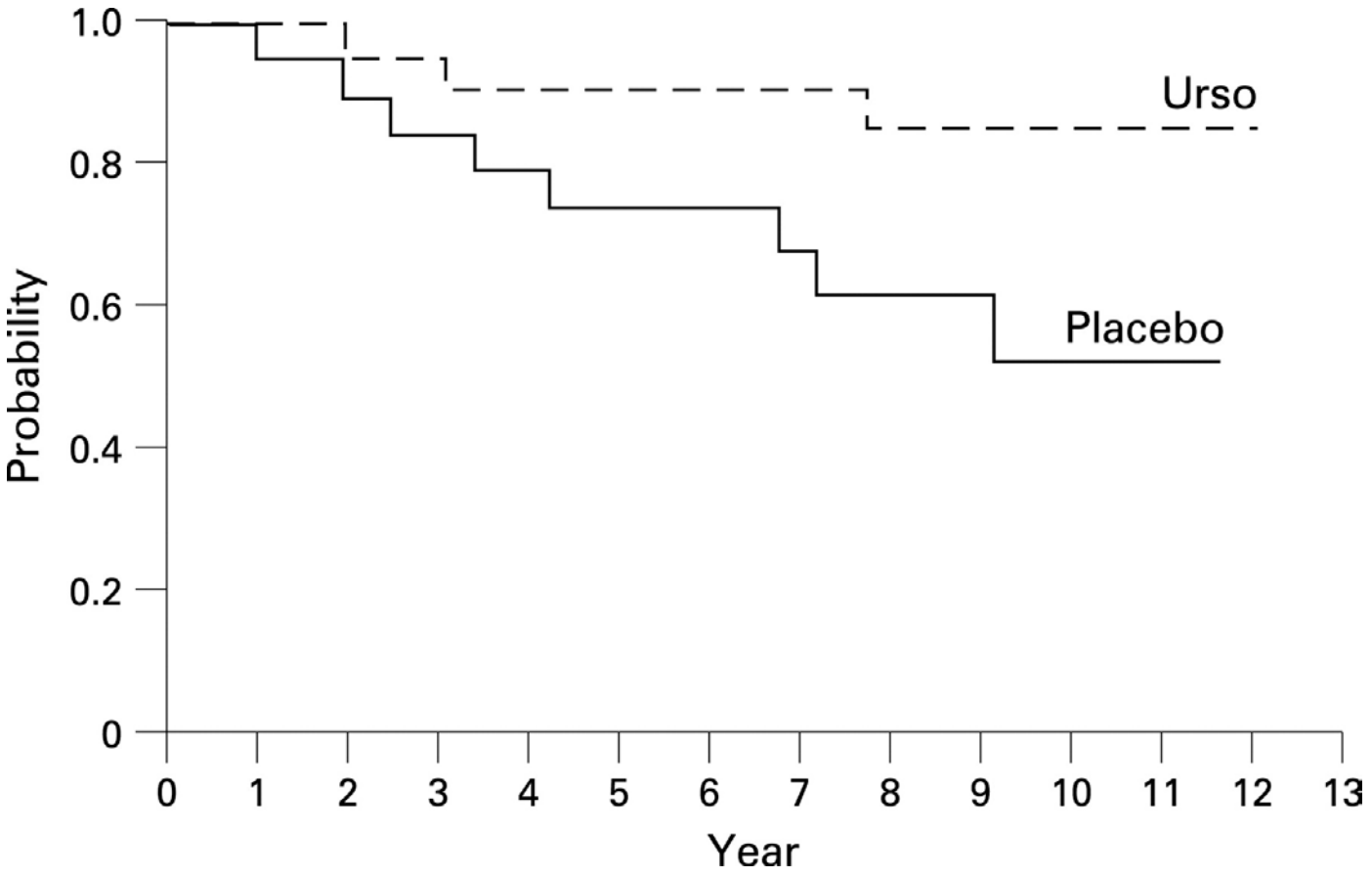
We're all different: one size for all might not fit

Kaplan–Meier estimates of proportion of patients without dysplasia and carcinoma after taking ursodeoxycholic acid (Urso) or placebo.



Pardi DS, Loftus EV, Jr, Kremers WK, et al . Ursodeoxycholic acid as a chemopreventive agent in patients with ulcerative colitis and primary sclerosing cholangitis. Gastroenterology 2003;124:889–93

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UDCA- Pro-Establishment…

- Safe (normal dose)
- Reduces liver biochemical inflammation
- Studies looking at survival are frought with challenges
- Can’t expect it cures but may slow down disease in a subgroup
- Continue to offer patients the choice of therapy at normal dose

Cochrane review

- Eight trials evaluated UDCA versus placebo or no intervention (592 patients). The eight randomised clinical trials have a high risk of bias.
- Patients were treated for three months to six years (median three years). The dosage of UDCA used in the trials ranged from low (10 mg/kg body weight/day) to high (28 to 30 mg/kg body weight/day).
- Ursodeoxycholic acid did not significantly reduce the risk of death (RR 1.00; 95% CI 0.46 to 2.20); treatment failure including liver transplantation, varices, ascites, and encephalopathy (RR 1.22; 95% CI 0.91 to 1.64); liver histological deterioration (RR 0.89; 95% CI 0.45 to 1.74); or liver cholangiographic deterioration (RR 0.60; 95% CI 0.23 to 1.57).
- Ursodeoxycholic acid significantly improved serum bilirubin (MD -14.6 µmol/litre; 95% CI -18.7 to -10.6), alkaline phosphatases (MD -506 IU/litre; 95% CI -583 to -430), aspartate aminotransferase (MD -46 IU/litre; 95% CI -77 to -16), and gamma-glutamyltranspeptidase (MD -260 IU/litre; 95% CI -315 to -205), but not albumin (MD -0.20 g/litre; 95% CI -1.91 to 1.50).
- Ursodeoxycholic acid was safe and well tolerated by patients with primary sclerosing cholangitis.

Table 4. Review of Previous Studies on UDCA in PSC

Study	n	RCT	Duration (*y*)	Dose (*mg/day*)	Laboratory tests	Histology	Symptoms	ERC	Survival
Hayashi[10]	1	−	2	600	+	0	NE	−	NE
Chazouillers[11]	15	−	0.5	750–1250	+	NE	0	NE	NE
O'Brien[12]	12	−	1.5	10/kg	+	NE	+	NE	NE
Beuers[13]	14	+	1	13–15/kg	+	+	0	NE	−
Stiehl[14]	27	−	1	750	+	NE	+	NE	NE
	20	+	0.25	750	+	NE	0	NE	−
	12	−	1	750	+	+	+	[a]	NE
De Maria[15]	40	+	2	600	0	NE	0	0	0
Lindor[6]	102	+	2.2	13–15/kg	+	0	0	NE	0
Van Hoogstraten[16]	48	−	2	10/kg	+	0	0	0	0
Mitchell[17]	26	+	2	20/kg	+	+	0	NE	NE
Harnois[18]	30	−	1	25–30/kg	+	NE	NE	NE	+[b]
Okolicsanyi[19]	86	−	≈4	8–13/kg	+	+	NE	NE	NE
Schramm[20c]	15	−	4.5	500–750	−	+	NE	[d]	[b]
Färkkilä[22e]	80	+	3	15/kg	+	+	NE	0	0
Stiehl[23f]	65	−	≈4	750	+	NE	NE	0	+[b]
Sterling[21g]	25	−	2	13–15/kg	0	0	0	0	0

Gastroenterology Volume 129, Issue 5, November 2005, Pages 1464-1472

Chazouillères *et al.*[44]	Prospective	15	750–1250 mg	6	Improved liver function and symptoms
O'Brien *et al.*[45]	Open-label	12	10 mg/kg	30	Improved liver function and symptoms
Beuers *et al.*[43]	Double-blind, placebo-controlled	6	13–15 mg/kg	12	Improved liver function and histology. No effect on symptoms
Lo *et al.*[175]	Double-blind placebo controlled	23	10 mg/kg	24	Improved liver function. No effect on symptoms or histology
Stiehl *et al.*[176]	Double-blind, placebo-controlled	20	750 mg	12–48	Improved liver function and histology. No effect on symptoms
De Maria *et al.*[177]	Double-blind placebo controlled	59	600 mg	24	No improvement in liver function
Lindor[47]	Double-blind, placebo-controlled	105	13–15 mg/kg	34	Improved liver function. No effect on histology and symptoms
Van Hoogstraten *et al.*[178]	Double-blind	48	10 mg/kg	24	Improved liver function. No effect on symptoms
Mitchell *et al.*[49]	Double-blind, placebo-controlled	26	20–25 mg/kg	24	Improved liver function, histology and cholangiography. No effect on symptoms. No survival benefit
Harnois *et al.*[179]	Open label	30	25–30 mg/kg	12	Improved liver function and survival compared with Mayo risk score
Okolicsanyi *et al.*[180]	Open-label, placebo-controlled	86	8–13 mg/kg	120	Improved liver function and symptoms. No effect on histology
Olsson *et al.*[50]	Multi-centre randomised Double-blind, placebo-controlled	219	17–23 mg/kg	60	Improved liver function. Nonsignificant trend towards increased survival. No effect on symptoms
Cullen *et al.*[51]	Pilot dose range study	30	10 mg/kg 20 mg/kg 30 mg/kg	24	Improved projected survival with low and standard dose. Significantly improved projected survival with high dose
Lindor *et al.*[48]	Multi-centre Double-blind, placebo-controlled	150	28–30 mg/kg	60	Improved liver function. No improvement in symptoms or histology. Discontinued early (6 years): significantly risk of death, need for liver transplant or development of varicies

Meta-analysis pre-Lindor 2009

Table 1 Baseline characteristics of trials included in meta-analysis

Study, year	Publication type	Control	No. patients (UDCA/control)	Mean age (years)	Duration (months)	UDCA dose	ITT basis
Beuers *et al.*, 1992[6]	Full text	Placebo	6/8	30/45.4	12	13–15 mg/kg/d	No
Lo *et al.*, 1992[18]	Abstract	Placebo	8/10	NR	24	10 mg/kg/d	No
Stiehl *et al.*, 1994[7]	Full text	Placebo	10/10	36/41	3	750 mg/d	Yes
De Maria *et al.*, 1996[19]	Full text	No treatment	20/20	32.0/31.2	24	600 mg/d	No
Bansi *et al.*, 1996[20]	Abstract	Placebo	12/11	NR	12	20 mg/kg/d	No
Lindor, 1997[9]	Full text	Placebo	53/52	41.7/43.8	26*	13–15 mg/kg/d	Yes
Mitchell *et al.*, 2001[8]	Full text	Placebo	13/13	52/52	24	20 mg/kg/d	Yes
Olsson *et al.*, 2005[21]	Full text	Placebo	110/109	43.6/43.1	60	17–23 mg/kg/d	Yes

*Mean.
ITT, intention-to-treat; NR, not reported; UDCA, ursodeoxycholic acid.

Hepatology Research 2009; **39**: 865–873