Traitement médical, place de l'acide ursodésoxycholique

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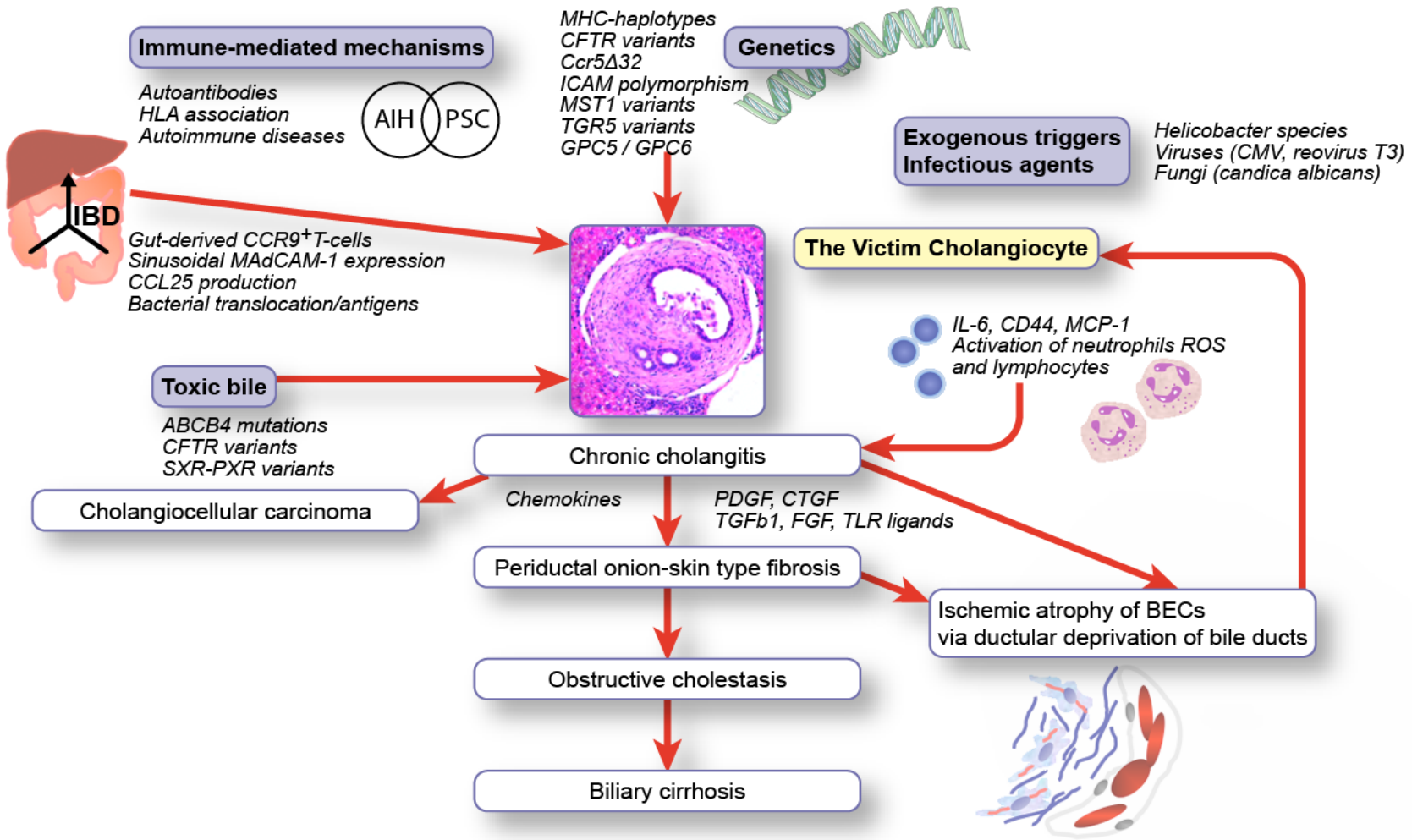
Points clés

- 8 essais thérapeutiques ont évalué l'AUDC comme traitement médical de la CSP. 7 essais avec AUDC, 13 - 23 mg/kg/j, 1 essai avec AUDC 28-30 mg/kg/j
- Tous les essais ont montré un effet positif sur la bilirubinémie à l'exception de l'essai AUDC 28-30 mg/kg/j
- Aucun des essais AUDC 13-23 mg/kg n'a montré d'effet bénéfique ou délétère en terme de survie sans transplantation. L'essai AUDC 28-30 mg/kg/j a montré un effet délétère en utilisant un score composite d'aggravation.
- Nous recommandons l'utilisation d'AUDC dans le traitement de la CSP à la dose de 13-17 mg/kg/j. Nous déconseillons les doses plus élevées en particulier chez les patients ayant une ou plusieurs sténoses dominantes ou une fibrose biliaire extensive.

PSC: pathobiology in brief



UDCA-controlled trials: Baseline characteristics

Study, year	Publication type	No. Patients (UDCA/control)	Mean age (years)	Duration (months)	UDCA
Beuers et al., 1992	Full text	6/8	30/45.4	12	13–15 mg/kg/d
Lo et al., 1992	Abstract	8/10	NR	24	10 mg/kg/d
Stiehl et al., 1994	Full text	10/10	36/41	3	750 mg/d
Bansi et al., 1996	Abstract	12/11	NR	12	20 mg/kg/d
Lindor, 1997	Full text	53/52	41.7/43.8	26*	13–15 mg/kg/d
Mitchell et al., 2001	Full text	13/13	52/52	24	20 mg/kg/d
Olsson et al., 2005	Full text	110/109	43.6/43.1	60	17–23 mg/kg/d

*: mean

Shi et al. Hepatology Research 2009

Effect on symptoms and biochemical values of UDCA treatment

Study, year	Fatigue	Pruritus	AST	ALT	γ-GT	ALP	Bilirubin	Albumin	Mayo score
Beuers et al., 1992	-	-	++	++	++	++	++	NR	+
Lo et al., 1992	-	-	+	NR	+	+	+	NR	NR
Stiehl et al., 1994	-	-	NR	++	++	++	+	-	-
Bansi et al., 1996	-	-	+	NR	++	++	+	-	NR
Lindor, 1997	NR	NR	++	NR	NR	++	++	-	NR
Mitchell et al., 2001	-	-	+	NR	++	++	+	-	NR
Olsson et al., 2005	NR	-	NR	+	NR	+	+	-	NR

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Clinical events

Study, year	Death[a]	Liver transplantation[a]	Death/ Liver transplantation[a]	Cholangiocarcinoma[a]
Beuers et al., 1992	0/1	0/0	0/1	0/0
Lo et al., 1992	0/0	0/0	0/0	0/0
Stiehl et al., 1994	0/0	0/0	0/0	0/0
Bansi et al., 1996	0/0	0/0	0/0	0/0
Lindor, 1997	4/3	9/8	13/11	0/3
Mitchell et al., 2001	0/1	1/0	1/1	0/0
Olsson et al., 2005	2/3	5/8	7/11	3/4

a: UDCA/control

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Histological and cholangioghraphic changes

Study, year	Histological improvement[a]	Histological deterioration[a]	Cholangioghraphic improvement[a]	Cholangioghraphic deterioration[a]
Beuers et al., 1992	2/0	0/1	NR	NR
Lo et al., 1992	NR	NR	NR	NR
Stiehl et al., 1994	NR	NR	0/0	0/1
Bansi et al., 1996	NR	NR	NR	1/0
Lindor, 1997	NR	8/3	NR	NR
Mitchell et al., 200	3/0	2/5	5/2	2/6
Olsson et al., 2005	NR	NR	NR	5/8

a: UDCA/control, NR: not reported

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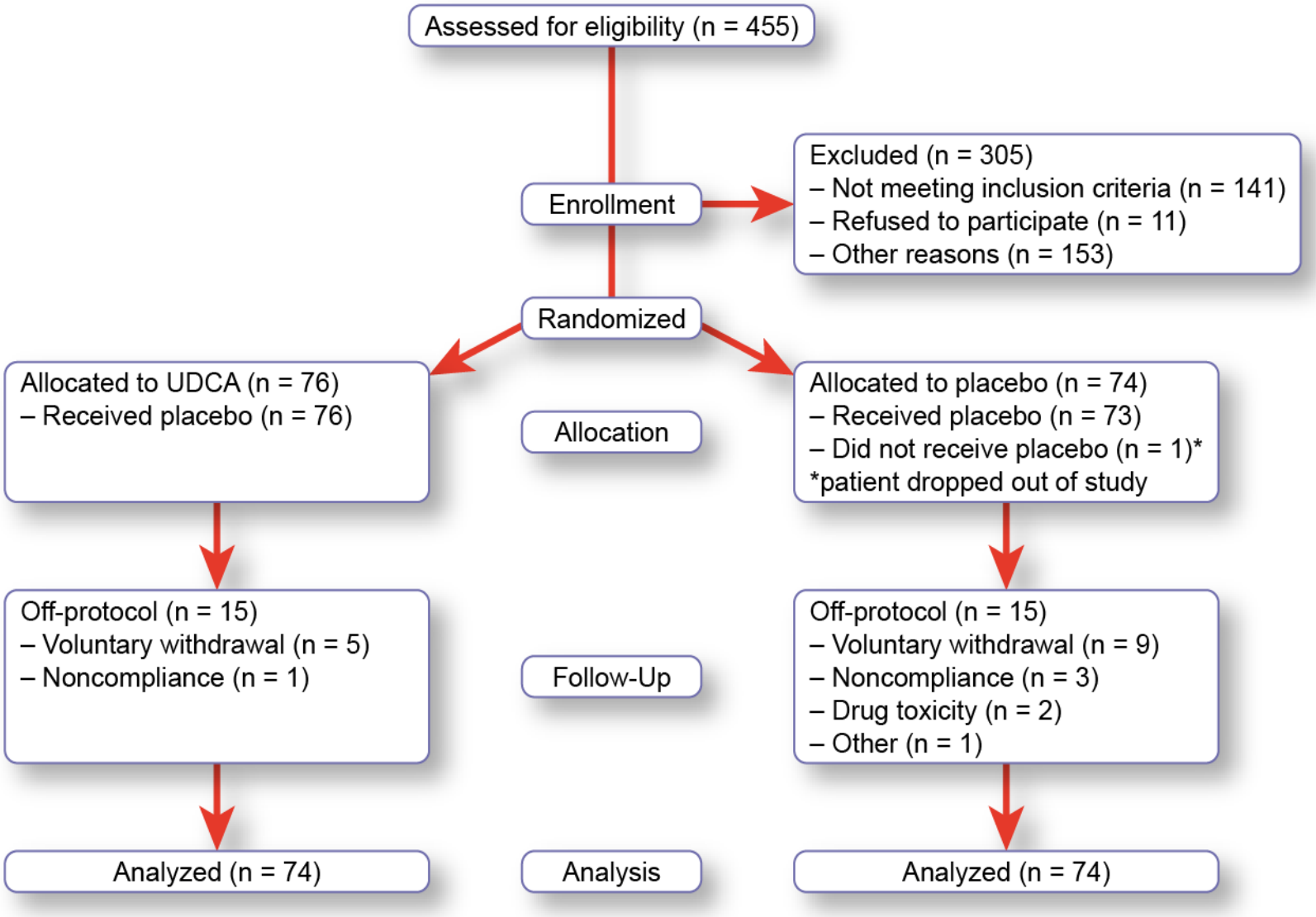
Meta-analysis of clinical events, liver histological and cholangioghraphic changes

	Studies (n)	Numbers in the UDCA group	Numbers in the control group	Odds ratio (95% CI)	P-value
Death	8	6/232	8/233	0.88 (0.30,2.60)	0.82
Liver transplantation	8	15/232	16/233	0.92 (0.44,1.92)	0.82
Death/liver transplantation	8	21/232	24/233	0.85 (0.45,1.61)	0.62
Cholangiocarcinoma	8	3/232	7/233	0.45 (0.12,1.63)	0.22
Adverse events	6	43/202	39/203	1.15 (0.68,1.95)	0.60
Histological improvement	3	5/39	0/41	9.19 (0.98,86.15)	0.05
Histological deterioration	4	10/92	9/93	1.14 (0.44,2.95)	0.78
Cholangioghraphic improvement	3	5/43	2/43	3.44 (0.53,22.43)	0.20
Cholangioghraphic deterioration	5	8/165	15/163	0.51 (0.22,1.22)	0.13

Shi et al. Hepatology Research 2009

- High dose UDCA for the treament of PSC
- Lindor L et al
- Hepatology, 2009.

Diagram of flow of patients through the study (Lindor K, 2009)



Lindor et al. Hepatology 2009

Clinical and laboratory characteristics: Patients at entry

Characteristic	UDCA (n = 76)	Placebo (n = 74)	P Value
Age, years	47.9 (20.5–75.6)	45.3 (17.9–73.6)	0.219
Duration of disease, years	1.3 (0.1–13.4)	1.0 (0.0–49.5)	0.833
Female sex, n (%)	38 (50)	26 (35)	0.066
Colitis, n (%)	55 (72)	61 (82)	0.14
Varices, n (%)	13 (17)	13 (18)	
Histologic stage, n (%)			
I	27 (36)	23 (31)	0.564
II	19 (25)	21 (28)	0.640
III	20 (26)	17 (23)	0.635
IV	10 (13)	13 (18)	0.454
Alkaline phosphatase*	3.3 (0.7–11.2)	3.2 (0.5–16.9)	0.814
AST*	2.0 (0.5–6.9)	2.3 (0.5–9.4)	0.684
Bilirubin, mg/dL	0.8 (0.2–3.2)	1.0 (0.2–5.5)	0.100
Mayo risk score	0.3 (-1.4–2.4)	0.3 (-1.5–2.5)	0.483

Data are presented as the median (range) unless otherwise indicated,
*Values represent multiples of the upper limits of normal

Lindor et al. Hepatology 2009

Biochemical labs

	UDCA	Placebo	P Value
Baseline (n)	76	73	
Alkaline Phosphatase	3.3 (0.7–11.2)	3.2 (0.5–16.9)	0.814
Aspartate Aminotransferase	2.0 (0.5–6.9)	2.3 (0.5–9.4)	0.684
Bilirubin	0.8 (0.2–3.2)	1.0 (0.2–5.5)	0.100
12 Months	70	63	
Alkaline Phosphatase	1.9 (0.6–9.1)	2.9 (0.6–13.6)	<0.001
Aspartate Aminotransferase	1.0 (0.5–10.5)	1.9 (0.6–8.7)	<0.001
Bilirubin	0.8 (0.2–6.3)	0.9 (0.3–8.2)	0.074
24 Months	65	59	
Alkaline Phosphatase	1.8 (0.6–8.5)	2.6 (0.5–11.9)	0.001
Aspartate Aminotransferase	1.1 (0.4–8.4)	1.9 (0.5–13.3)	<0.001
Bilirubin	0.8 (0.2–7.2)	1.0 (0.2–8.6)	0.393
36 Months	56	53	
Alkaline Phosphatase	1.7 (0.6–16.5)	2.4 (0.4–12.1)	0.012
Aspartate Aminotransferase	1.1 (0.3–7.2)	1.7 (0.5–14.8)	<0.001
Bilirubin	0.8 (0.2–15.9)	0.9 (0.3–9.6)	0.037

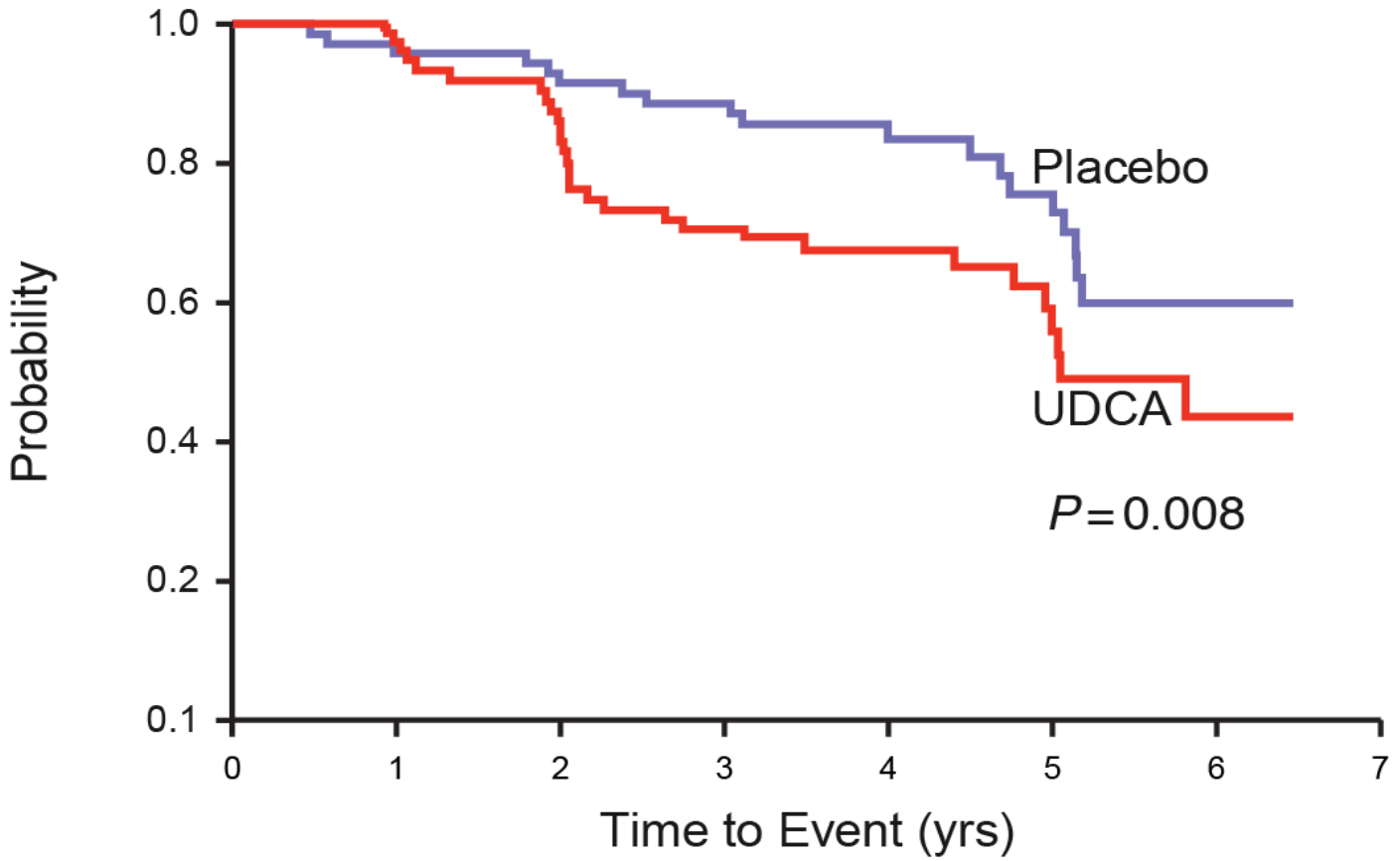
Lindor et al. Hepatology 2009

Development of primary endpoints

Primary Endpoints	UDCA	Placebo
Death	5	3
Liver transplantation	11	5
Minimal listing criteria for liver transplantation	13	10
Development of cirrhosis	6	4
Esophageal and/or gastric varices	15	5
Cholangiocarcinoma	2	2
Total endpoints	52	29
Number of patients reaching a primary endpoint	30	19
Number of patients reaching death, orthotopic liver transplantation, minimal criteria listing	22	15

Lindor et al. Hepatology 2009

Kaplan-Meier curve for time until reaching primary end-points



Placebo	76	73	60	51	34	18	9	0
UDCA	74	65	60	58	41	24	7	0

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Models

	Hazard Ratio (UDCA versus Placebo)	(95% CI)	P Value
Adjusted for stratification variables: Mayo risk score, baseline presence of varices, and histologic stage			
Primary endpoints	2.27	(1.24–4.16)	0.008
Death, liver transplantation or minimal criteria for listing	2.11	(1.04–4.28)	0.038
Adjusted for Mayo risk score, varices, histologic stage, age, sex, inflammatory bowel disease, alkaline phosphatase, aspartate aminotransferase, and bilirubin			
Primary endpoints	2.73	(1.37–5.38)	0.004
Death, liver transplantation or minimal criteria for listing	2.85	(1.26–6.49)	0.012

Lindor et al. Hepatology 2009

Changes in bile acids in patients with a clinical endpoint.

Patient No.	ΔDCA (µlmol/L)	ΔCA (µlmol/L)	ΔCDCA (µlmol/L)	ΔUDCA (µlmol/L)	ΔLCA (µlmol/L)	ΔtBA (µlmol/L)
1	–0.05	–0.05	0.52	4.58	–0.13	4.87
2	0.01	–0.02	0.34	5.25	0.32	5.73
3	–0.1	–0.21	–0.17	13.92	0.20	13.62
4	0.08	0.62	2.80	80.05	0.14	83.72
5	0.08	–0.44	–0.24	–0.07	0.05	–0.64
6	0.27	1.07	1.61	74.11	1.28	78.33
7	0.11	–0.54	–0.23	3.65	0.83	3.77
8	–0.01	–0.18	0.01	9.99	–0.01	9.79
9	–0.01	–0.17	0.22	115.72	0.03	115.79

Sinakos et al. Hepatology 2010

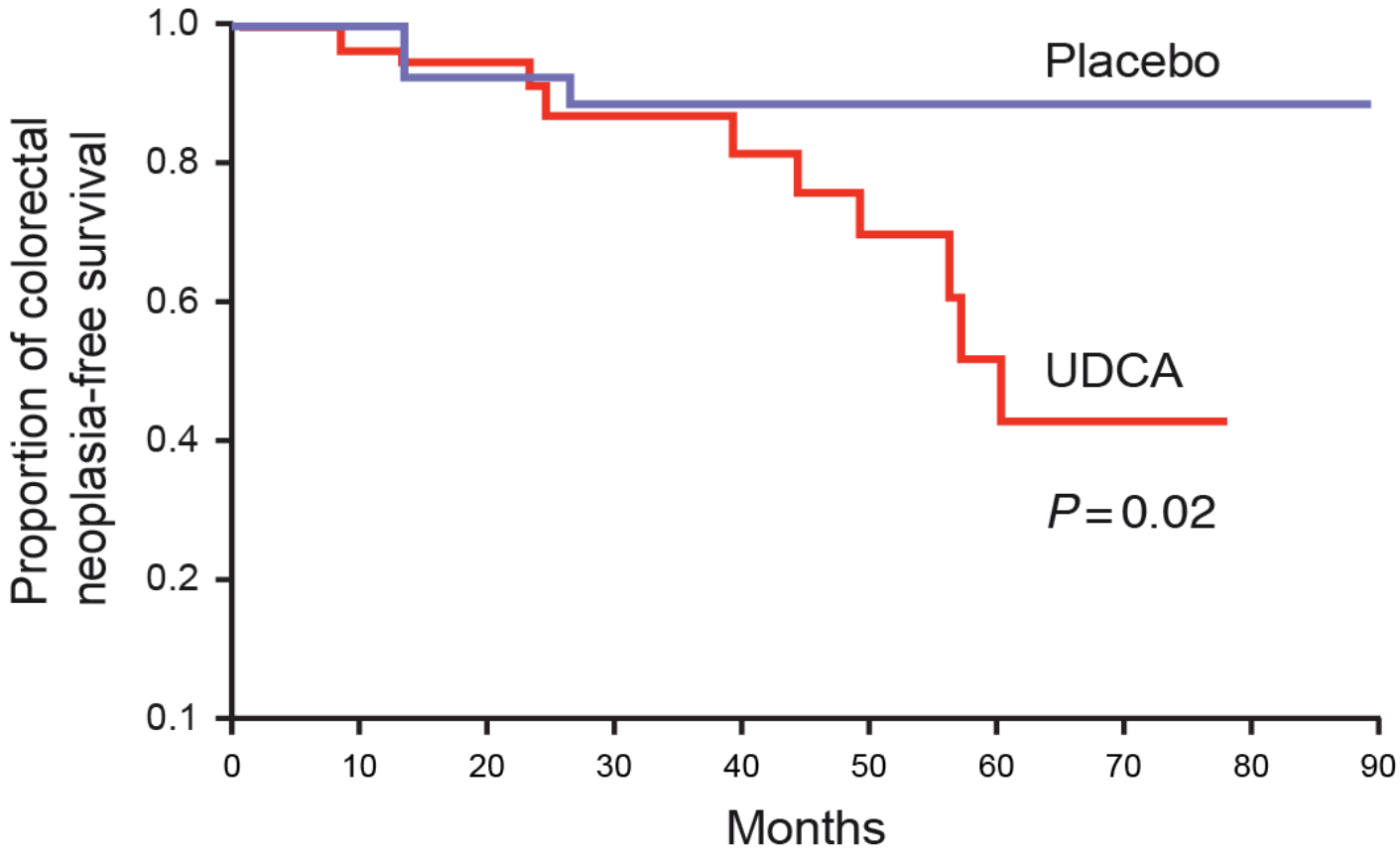
- High-dose UDCA is associated with the development of colorectal neoplasia in patients with Ulcerative colitis and primary sclerosing cholangitis
- Eaton JE et al :Am J Gastroenterol,2011.

Clinical features of the study patients according to randomization groups

	UDCA (25)	Placebo (31)	N	P value
Age at study entry	45 (21 – 77)	45 (18 – 64)	56	NS
Gender			56	
Male	64 % (16 / 25)	58 % (18 / 31)		NS
Female	36 % (9 / 25)	42 % (13 / 31)		NS
BMI	26 (13 – 35)	26 (19 – 44)	54	NS
Smoking history	11 % (2 / 18)	13 % (3 / 23)	41	NS
Family history colon cancer	0 % (0 / 18)	4 % (1 / 23)	41	NS
5-ASA use	78 % (14 / 18)	93 % (25 / 27)	45	NS
Immunomodulator use	0 % (0 / 13)	5 % (1 / 18)	31	NS
Steroid use	0 % (0 / 13)	6 % (1 / 18)	31	NS
NSAID use	29 % (4 / 14)	22 % (4 / 18)	32	NS
Non-dietary folic acid use	0 % (0 / 14)	11 % (2 / 18)	32	NS
Age at diagnosis of PSC	38 (20 – 71)	39 (17 – 64)	56	NS
PSC duration (months)	75 (1 – 299)	49 (1 – 603)	56	NS
Histologic stage			56	
I	36 % (9 / 25)	26 % (8 / 31)		NS
II	28 % (7 / 25)	42 % (13 / 31)		NS
III	24 % (6 / 25)	16 % (5 / 31)		NS
IV	12 % (3 / 25)	16 % (5 / 31)		NS
UC duration (years)	11 (0 – 34)	8 (0 – 38)	56	NS
Severity of colitis			53	
Inactive	13 % (3 / 23)	10 % (3 / 30)		NS
Mild	65 % (15 / 23)	53 % (16 / 30)		NS
Moderate	17 % (4 / 23)	37 % (11 / 30)		NS
Severe	4 % (1 / 23)	0 % (0 / 30)		NS
Pancolitis	90 % (19 / 21)	90 % (26 / 29)	50	NS
Surveillance biopsies	30 ± 6.8	31 ± 5.6	41	NS

Eaton et al. Am J Gastroenterol 2010

Proportion of patients free of colorectal neoplasia according to randomization group



Eaton et al. Am J Gastroenterol 2010

The role of covariates in the development of cancer or dysplasia

Variable	Univariate		Multivariate	
	HR (95 % CI)	P value	HR (95 % CI)	P value
Age at study entry	1.03 (0.99 – 1.08)	0.16	—	—
Gender female vs. Male	0.89 (0.24 – 2.85)	0.86	—	—
BMI	0.98 (0.85 – 1.10)	0.72	—	—
Smoking history	0 (–)	0.10	0 (–)	0.10
Family history of colon cancer	0 (–)	0.42	—	—
5-ASA use	1.24 (0.22 – 23.20)	0.84	—	—
Immunomodulator use	0 (–)	0.50	—	—
Steroid use	0 (–)	0.50	—	—
NSAID use	1.96 (0.27 – 10.06)	0.46	—	—
Non-dietary folic acid use	0 (–)	0.29	—	—
UDCA	4.44 (1.30 – 20.10)	0.02	5.97 (1.39 – 41.44)	0.02
Age at diagnosis of PSC	1.02 (0.97 – 1.07)	0.40	—	—
PSC duration (months)	1.00 (0.99 – 1.00)	0.75	—	—
Histologic stage (I – IV)	1.06 (0.61 – 1.81)	0.83	—	—
UC duration (years)	1.04 (0.99 – 1.09)	0.10	1.05 (0.98 – 1.13)	0.16
UC severity (inactive – severe)	0.68 (0.28 – 1.68)	0.40	—	—
Pancolitis	0.39 (0.10 – 2.55)	0.28	—	—

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Change in serum bile acid composition before and after therapy with high-dose UDCA

	LCA (µmol / l)	DCA (µmol / l)	UDCA (µmol / l)	CDCA (µmol / l)	CA (µmol / l)	Total B (µmol / l)
Patients on UDCA with colorectal neoplasia (n=4)	0.6 ± 0.6	0.1 ± 0.1	21.9 ± 34.8	0.6 ± 0.8	0.1 ± 0.4	23.2 ± 36.8
Patients on UDCA without colorectal neoplasia (n=10)	0.2 ± 0.2	0.1 ± 0.2	16.9 ± 35.9	0.1 ± 0.3	0.01 ± 0.7	17.1 ± 36.1
P value	0.28	0.72	0.43	0.22	0.88	0.28

Data represent change from baseline and are expressed as means ± s.d.

Eaton et al. Am J Gastroenterol 2010

Effect of the baseline characteristics on the bile acid composition

	DCA (µlmol/L)	CA (µlmol/L)	CDCA (µlmol/L)	UDCA (µlmol/L)	LCA (µlmol/L)
Colectomy (n = 12)	0.07 ± 0.05	0.54 ± 0.55	0.32 ± 0.25	0.07 ± 0.09	0.08 ± 0.07
No colectomy (n = 44)	0.27 ± 0.22	0.76 ± 2.44	0.40 ± 0.88	0.13 ± 0.14	0.11 ± 0.07
P value	<0.0001	NS	NS	NS	NS
Alkaline phosphatase < 4 x ULN (n = 28)	0.27 ± 0.25	0.95 ± 3.06	0.46 ± 1.09	0.10 ± 0.10	0.12 ± 0.06
Alkaline phosphatase ≥ 4 x ULN (n = 28)	0.18 ± 0.16	0.47 ± 0.42	0.30 ± 0.22	0.14 ± 0.15	0.09 ± 0.08
P value	NS	0.03	NS	NS	NS
Total bilirubin < 0.9 mg/dL (n = 27)	0.25 ± 0.22	0.36 ± 0.46	0.26 ± 0.24	0.08 ± 0.06	0.10 ± 0.08
Total bilirubin ≥ 0.9 mg/dL (n = 29)	0.20 ± 0.21	1.03 ± 2.98	0.49 ± 1.06	0.15 ± 0.16	0.11 ± 0.06
P value	NS	0.05	NS	NS	NS

The data are presented as means and standard deviations

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UDCA combined with other therapies

• UDCA + methotrexate	Lindor, 1996
• UDCA + steroids	Schramm, 1999 van Hoogstraten, 2000
• UDCA + MMF	Sterling, 2004
• UDCA + metronidazole	Färkkilä, 2004
• UDCA + endoscopic therapy	Stiehl, 2007