TREATMENT OF

PRIMARY BILIARY CIRRHOSIS (PBC)

URSO not indicated

Therapy for PBC Difficulties

- Etiology is uncertain
- Therapies are based on ideas regarding pathogenesis
- Present medical therapies have a limited effect

• Advanced cases: Liver transplantation may be the only option

Pathogenetic features of Primary Biliary Cirrhosis (PBC)

- Immuno-inflammatory destruction of small intrahepatic bile ducts
- "The florid duct lesion"
- Progressive cholestasis
- Cirrhosis
- Liver failure

Ursodeoxycholic acid (UDCA)

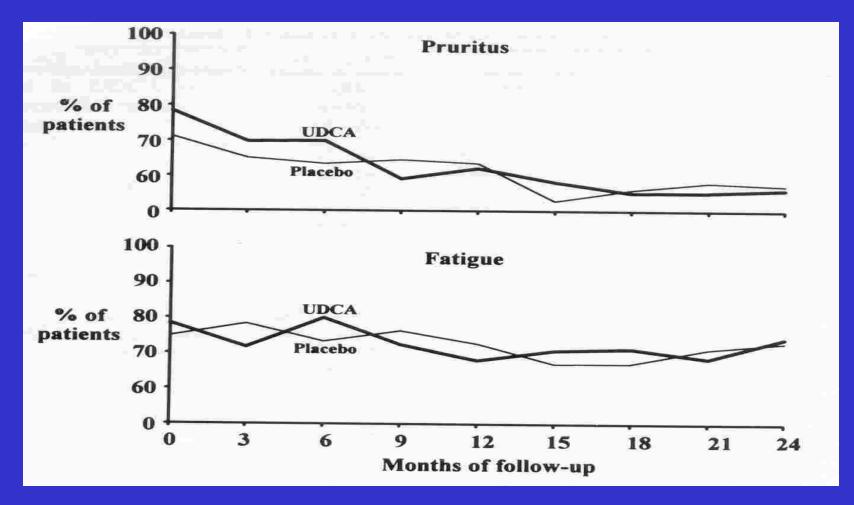
- UDCA is hydrophilic bile acid, constituting in man only 1-3% of biliary bile acids.
- UDCA is less hepatotoxic than other bile acids.
- By administering UDCA orally the concentration of UDCA in bile increases and the bile becomes less toxic.
- This may reduce the tissue damaging effects of bile leaking from damaged bile ducts.

RCTs of Ursodeoxycholic acid (UDCA) Cochrane Database Syst Rev. 2002;(1):CD000551

- UDCA (8-15 mg/kg/day) for 3 months to five years.
- 16 RCTs against placebo (n=15) or no intervention (n=1) in 1422 patients.
- UDCA significantly (P<0.05) reduced ascites, jaundice, serum bilirubin and liver enzymes.
- UDCA had no significant effects on mortality, liver transplantation, mortality or liver transplantation, pruritus, fatigue, s-albumin, prothrombin time, quality of life, liver histology, or portal pressure.

Effect of UDCA on Pruritus and Fatigue

Heathcote J et al. UDCA (14 mg/kg/day) 111 pts. Hepatology 1994;19:1149-56. Placebo 111 pts.



PBC: The effect of UDCA on mortality

Cochrane Database Syst Rev. 2002;(1):CD000551

C St	udy	UDCA n/N	Control n/N		Peto OR (95%Cl Fixed)	Weight %	Peto OR (95%Cl Fixed)
88	ATHENS	17/43	14/43			26.4	1.35[0.56,3.24]
	BARCELONA	10/99	4/93		-	17.2	2.35[0.79,6.95]
	DALLAS	3/77	3/74			- 7.6	0.96[0.19,4.89]
×	FRANKFURT	0/10	0/10			0.0	Not Estimable
	GÖTEBORG	1/60	1/56	<u> </u>	-	→ 2.6	0.93[0.06,15.12]
	HELSINKI	0/30	2/31	~ •		2.6	0.14[0.01,2.21]
	MAYO-I	4 / 89	7/91	35		13.7	0.57[0.17,1.94]
×	MILAN	0/44	0/44			0.0	Not Estimable
×	NEVVARK-II	0/9	0/10			0.0	Not Estimable
	NEVVCASTLE	1/22	3/24	<	-	4.9	0.38[0.05,2.86]
×	TAIPEI	0/6	0/6			0.0	Not Estimable
×	TOKYO	0/26	0/26			0.0	Not Estimable
	TORONTO	5/111	9/111	345		17.4	0.54[0.19,1.60]
	VILLEJUIF	3/73	3/73	100		- 7.6	1.00[0.20,5.10]
Тс	otal(95%Cl)	44 / 699	46 / 692			100.0	0.94[0.60,1.48]
Τe	est for heterogeneity chi-s	square=7.63 df=8 p=0.4	47				
Τe	est for overall effect z=-0	0.26 p=0.8					
83				.1 .2 UDCAbett	1	5 10 CAworse	

PBC: Effect of UDCA on transplantation

Cochrane Database Syst Rev. 2002;(1):CD000551

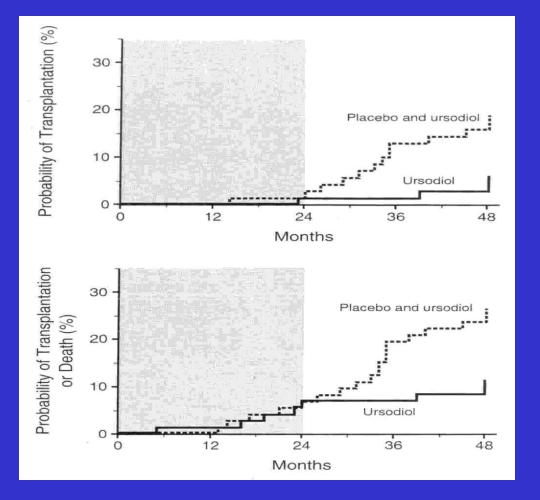
Comparison: 01 Efficacy - UDCA versus placebo or no intervention **Outcome:** 02 Liver transplantation Weight Peto OR UDCA Control Peto OR Study n/N n/N (95%CI Fixed) % (95%Cl Fixed) ATHENS 4/43 3/43 1.36[0.29,6.32] 9.2 7/99 18.4 BARCELONA 7/93 0.94[0.32,2.77] 8/74 1.09[0.40,2.98] DALLAS 9/77 21.5 FRANKFURT. Not Estimable 0/10 0/10 0.0 GÖTEBORG 2/60 3/56 0.61[0.10,3.67] 6.8 3/31 0.13[0.01,1.31] HELSINKI 0/30 4.1 3/89 5/91 0.61[0.15,2.50] MAYO-I 10.9 0/44 MILAN. 0/440.0 Not Estimable 0/9 0/10 NEWARK-II. 0.0 Not Estimable NEWCASTLE 2122 1/24 4.0 2.20[0.22,22.37] 0/6 TAIPEL 0/6 0.0 Not Estimable 0/26 Not Estimable TOKYO 0/26 0.0 7/111 10/111 0.68[0.25,1.83] TORONTO. 22.3 1.00[0.06,16.14] VILLEJUIF 1/73 1/73 2.8 41/692 100.0 Total(95%Cl) 35/699 0.83[0.52,1.32] Test for heterogeneity chi-square=4.35 df=8 p=0.82 Test for overall effect z=-0.79 p=0.4 2 5 10 .1 **UDCAbetter** UDCA worse

PBC: Effect of UDCA on mortality or transplantation

Cochrane Database Syst Rev. 2002;(1):CD000551

tudy	UDCA n/N	Control n/N	Peto OR (95%Cl Fixed)	Weight %	Peto OR (95%Cl Fixed)
ATHENS	21 / 43	17 / 43		15.5	1.45[0.62,3.38]
BARCELONA	17/99	11/93		17.3	1.53[0.69,3.41]
DALLAS	12/77	11/74	a	14.1	1.06[0.44,2.56]
FRANKFURT	0/10	0/10		0.0	Not Estimable
GÖTEBORG	3/60	4/56		4.8	0.69[0.15,3.15]
HELSINKI	0/30	5/31	< <u> </u>	3.4	0.12[0.02,0.75]
MANCHESTER	4/14	2/14		→ 3.5	2.27[0.38,13.34
MAYO-I	7/89	12/91		12.3	0.57[0.22,1.47]
MILAN	0/44	0/44	0.5 0.00 E 200	0.0	Not Estimable
NEWARK-II	0/9	0/10		0.0	Not Estimable
NEWCASTLE	3/22	4/24	······································	4.4	0.79[0.16,3.91]
TAIPEI	0/6	0/6		0.0	Not Estimable
токуо	0/26	0/26		0.0	Not Estimable
TORONTO	12/111	19/111		19.3	0.59[0.28,1.26]
VILLEJUIF	4/73	4/73		5.5	1.00[0.24,4.14]
otal(95%Cl)	83/713	89/706		100.0	0.90[0.65,1.26]
est for heterogeneity chi-	square=10.99 df=9 p=0).28			
est for overall effect z=-	0.59 p=0.6				

RCT with the most marked effect of UDCAPoupon R et al.N Engl J Med 1994;330:1342-7.Placebo: 72 pts.UDCA (13-15 mg/kg/day): 73 pts.



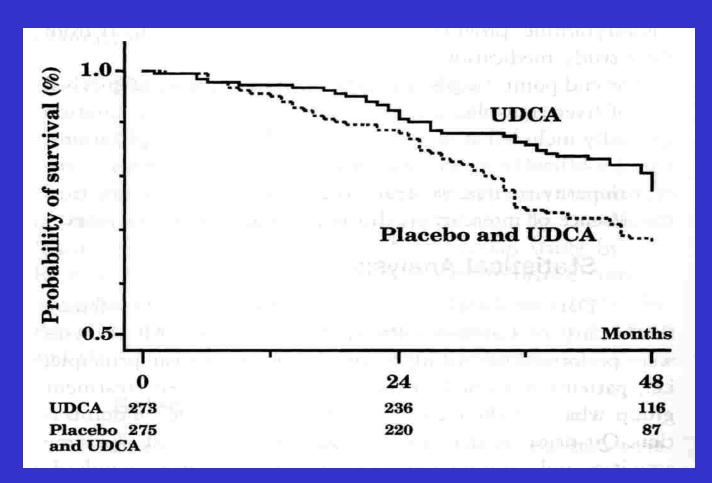
The excess endpoints in the placebo group occurs after "crossover", i.e. **during** UDCA therapy.

The excess endpoints are transplantations, not deaths.

"Cross-over" from Placebo to UDCA after 2 years

Poupon R et al.

Gastroenterology 1997;113:884-90.



The excess endpoints in the Placebo group occurs *during* UDCA treatment

PBC: The effect of UDCA on mortality including "cross-over" data Cochrane Database Syst Rev. 2002;(1):CD000551

Comparison: 04 UDCA-UDCA versus placebo/no intervention-UDCA Outcome: 01 Mortality

Outcome: 01 Mon	UDCA	Control	Peto OR	Weight	Peto OR
Study	n/N	n/N	(95%Cl Fixed)	%	(95%Cl Fixed)
01 Jadad score = 4 or 5			· · · · · · · · · · · · · · · · · · ·		
BARCELONA	10/99	4/93		11.2	2.35[0.79,6.95]
× FRANKFURT	0/10	0/10		0.0	Not Estimable
GÖTEBORG	1/60	1/56	<	→ 1.7	0.93[0.06,15.12]
HELSINKI	0/30	2/31	<	1.7	0.14[0.01,2.21]
MAYO-I	6/89	8/91		11.1	0.75[0.25,2.23]
× MILAN	0/44	0/44		0.0	Not Estimable
TORONTO	20/111	17/111		26.6	1.21[0.60,2.45]
Subtotal(95%Cl)	37 / 443	32/436		52.3	1.17[0.71,1.93]
Test for heterogeneity chi-s	square=4.54 df=4 p=0.3	34			
Test for overall effect_z=0.	60 p=0.5				
02 Jadad score = 1, 2 or 3					
ATHENS	17/43	14/43		17.2	1.35[0.56,3.24]
DALLAS	11/77	9/74		15.0	1.20[0.47,3.07]
X NEWARK-II	0/9	0/10		0.0	Not Estimable
NEWCASTLE	1/22	3/24	<	3.2	0.38[0.05,2.86]
× TAIPEI	0/6	0/6		0.0	Not Estimable
X TOKYO	0/26	0/26		0.0	Not Estimable
VILLEJUIF	6/73	10/73		12.3	0.57[0.20,1.61]
Subtotal(95%Cl)	35 / 256	36 / 256		47.7	0.96[0.57,1.62]
Test for heterogeneity chi-s	square=2.58 df=3 p=0.4	46			
Test for overall effect z=-0	0.16 p=0.9				
Total(95%Cl)	72/699	68 / 692		100.0	1.06[0.74,1.53]
Test for heterogeneity chi-s					1.00[0.14,1.00]
Test for overall effect z=0.		18			
	02 p-0.1				
104			.1 .2 1 UDAC better UD	Ś 1D)CAworse	

PBC: Effect of UDCA on transplantation including "cross-over" data Cochrane Database Syst Rev. 2002;(1):CD000551

Comparison: 04 UDCA-UDCA versus placebo/no intervention-UDCA

	r transplantation UDCA	Control	Peto OR	Weight	Peto OR
Study	n/N	n/N	(95%Cl Fixed)	%	(95%Cl Fixed)
01 Jadad score = 4 or 5					
BARCELONA	7/99	7/93		11.2	0.94[0.32,2.77]
× FRANKFURT	0/10	0/10		0.0	Not Estimable
GÖTEBORG	2/60	3/56	20 <u></u>	4.2	0.61[0.10,3.67]
HELSINKI	0/30	3/31	< a	2.5	0.13[0.01,1.31]
MAYO-I	7/89	7/91		11.2	1.02[0.35,3.04]
× MILAN	0/44	0/44		0.0	Not Estimable
TORONTO	15/111	22/111		26.7	0.64[0.31,1.29]
Subtotal(95%Cl)	31 / 443	42/436		55.8	0.70[0.43,1.14]
Test for heterogeneity chi-s	quare=2.88 df=4 p=0.58				
Test for overall effect z=-1	.42 p=0.16				
02 Jadad score = 1, 2 or 3					
ATHENS	4/43	3/43	12	- 5.6	1.36[0.29,6.32]
DALLAS	16/77	20/74		23.8	0.71[0.34,1.50]
X NEWARK-II	0/9	0/10	107.430	0.0	Not Estimable
NEWCASTLE	2/22	1/24		→ 2.5	2.20[0.22,22.37]
× TAIPEI	0/6	0/6		0.0	Not Estimable
X TOKYO	0/26	0/26		0.0	Not Estimable
VILLEJUIF	4/73	12/73		12.4	0.33[0.12,0.92]
Subtotal(95%Cl)	26 / 256	36 / 256		44.2	0.66[0.38,1.14]
Test for heterogeneity chi-s	quare=3.68 df=3 p=0.3				
Test for overall effect z=-1	.48 p=0.14				
	57/699	78/692		100.0	0.0010 40.0.001
Total(95%Cl)				100.0	0.68[0.48,0.98]
Test for heterogeneity chi-s Test for overall effect z=-2					
			E	5 10 Aworse	

PBC: Effect of UDCA on mortality or transplantation including "cross-over" data Cochrane Database Syst Rev. 2002;(1):CD000551

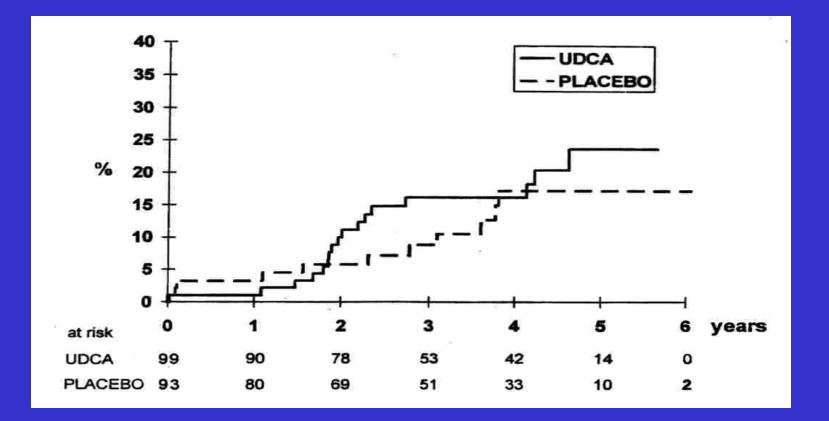
Comparison: 04 UDCA-UDCA versus placebo/no intervention-UDCA **Outcome:** 03 Mortality or liver transplantation UDCA Control Peto OR Weight Peto OR Study % n/N n/N (95%CI Fixed) (95%CI Fixed) 01 Jadad score = 4 or 5 BARCELONA 17/9911/93 11.7 1.53[0.69,3.41] FRANKFURT 0/10 0/10 0.0 Not Estimable GÖTEBORG 5/60 7/56 0.64[0.19,2.11] 5.3 HELSINKI 0/30 5/31 2.3 0.12[0.02.0.75] MAYO-I 13/8915/9111 5 0.87[0.39,1.94] MILAN 0/44 0/44 0.0 Not Estimable TORONTO 35/111 39/111 24.1 0.85[0.49,1.49] Subtotal(95%CI) 70/443 77/436 54.8 0.87[0.60,1.26] Test for heterogeneity chi-square=6.71 df=4 p=0.15 Test for overall effect z=-0.74 p=0.5 02 Jadad score = 1, 2 or 3 17/43 ATHENS 21/43 10.4 1.45[0.62,3.38] DALLAS 27 / 77 29/74 17.2 0.84[0.43.1.62] MANCHESTER 4/14 2/14 2.4 2.27[0.38,13.34] NEWVARK-II 0/9 0/10 0.0 Not Estimable 0.79[0.16,3.91] NEWCASTLE 3/22 4/24 2.9 TAIPEI 0/6 0/6 0.0 Not Estimable TOKYO 0/26 0/26 0.0 Not Estimable VILLEJUIF 10/7322/73 12.2 0.39[0.18,0.84] Subtotal(95%CI) 65/270 74/270 45.2 0.81[0.54,1.22] Test for heterogeneity chi-square=6.61 df=4 p=0.16 Test for overall effect z=-1.02 p=0.3 Total(95%Ch 135/713 151 / 706 100.0 0.84[0.64.1.11] Test for heterogeneity chi-square=13.38 df=9 p=0.15 Test for overall effect z=-1.23 p=0.2 2 .1 5 10

UDCAbetter

UDCAworse

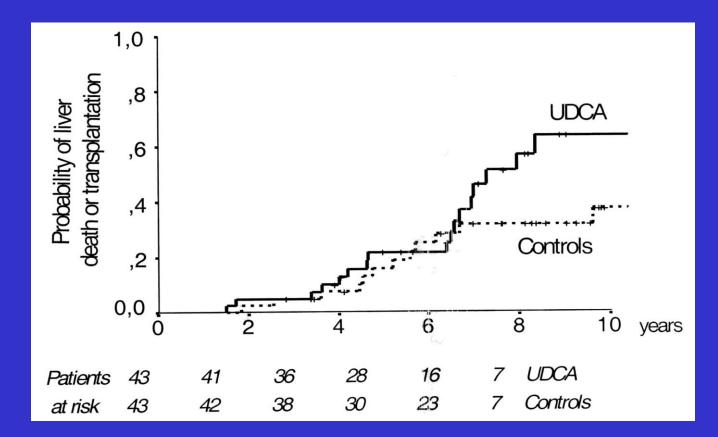
Long term UDCA therapy. Effect on mortality or liver transplantation (1)

Pares A et al.J Hepatol 2000; 32: 561-66.UDCA dose: 14-16 mg/kg/day



Long term UDCA therapy. Effect on mortality or liver transplantation (2)

Papatheodoridis G et al.Am J Gastroent 2002 (in press)UDCA dose: 12 -15 mg/kg/day



Medical therapies for primary biliary cirrhosis (PBC) tested in RCTs.

Therapy	Number of patients in RCT(s)	Effect
Cyclosporin A	390	+
Azathioprine	281	+
Prednisolone ¹	66	+
Prednisone + Azathioprine ¹	50	+
Budesonide ¹	39	+
Chlorambucil	24	+
Malotilate	101	(+)
Ursodeoxycholic acid (UDCA) (standard	dose) 1422	((+))
Colchicine ²	493	((+))
D-penicillamine	635	-
Methotrexate	99	-
Thalidomide	18	-

PBC: Azathioprine 1-2 mg/kg/day

• Heathcote (Gastroenterology 1976;70:656-60) 22 patients AZA (2 mg/kg/day) 23 untreated controls

• Multinational study (Gastroenterology 1985;89:1084-91) 124 patients AZA (1 mg/kg/day) 112 patients placebo

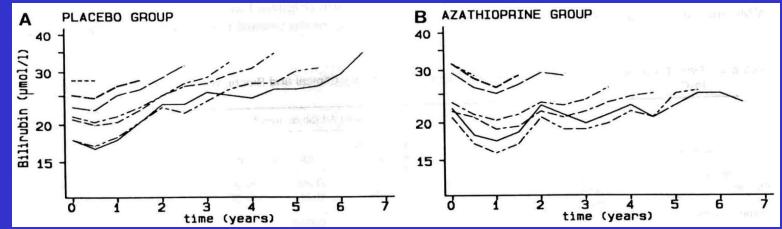
• AZA initially improved symptoms and biochemical tests.

- AZA significantly improved survival in the large study
- Side effects 10% more frequent during AZA.

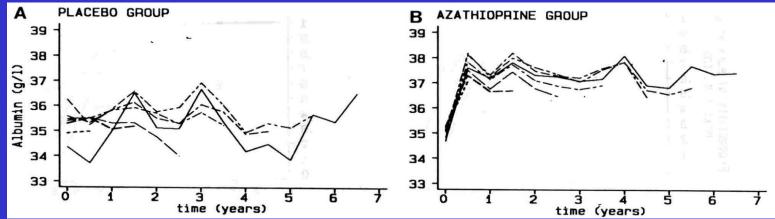
PBC: Effect of Azathioprine

Gastroenterology 1993;105:1865-76

Bilirubin:



Albumin:



PBC: Glucocorticosteroids

A: Mitchison (J Hepatol 1992; 15;336-44) 36 patients **Prednisolone** (30-10 mg/day) vs. placebo for 3 years.

B: Leuschner (J Hepatol 1996;25:29-57) 30 patients: **Prednisolone** (10 mg/day) vs. placebo for 9 months. (All on UDCA)

C: Leuschner (Gastroenterology 1999;117:918-25) 39 patients: **Budesonide** k (9 mg/day) vs. placebo for 2 years. (All on UDCA)

Steroid had <u>significantly beneficial effect</u> on "<u>overall hepatic assessment</u>" (hepatic deaths, doubling of bilirubin, >6 g/l reduction in albumin, new symptoms of portal hypertension and occurrence of cirrhosis) (prednisolone 21% placebo 65%) (A), <u>biochemistry and histology</u> (B and C). No significant adverse effect was found on bone mineral content.

PBC: Prednisone + Azathioprine

Wolfhagen FH.

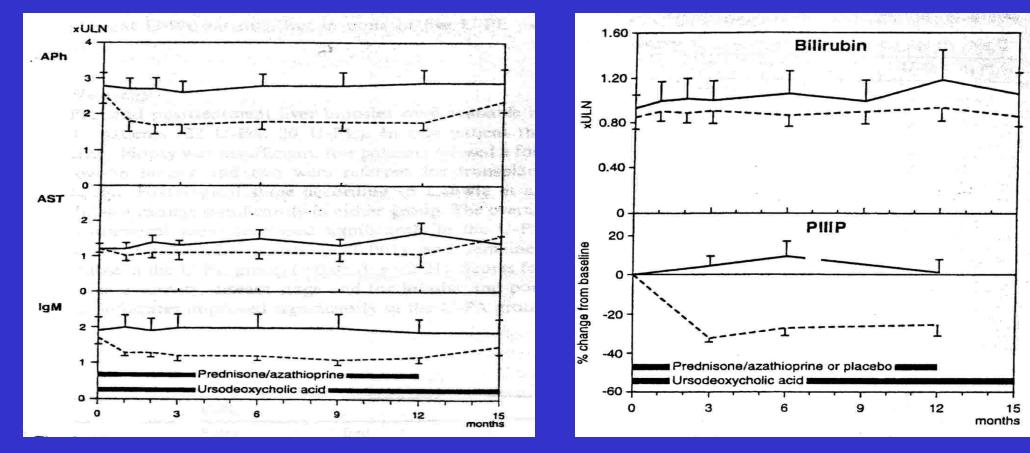
(J Hepatol 1998; 29:736-42)

50 patients treated for 1 year (all received UDCA). <u>Prednisone</u> (30-10 mg/day) plus <u>Azathioprine</u> (50 mg/day) vs. Placebo

Prednisone + azathioprine led to

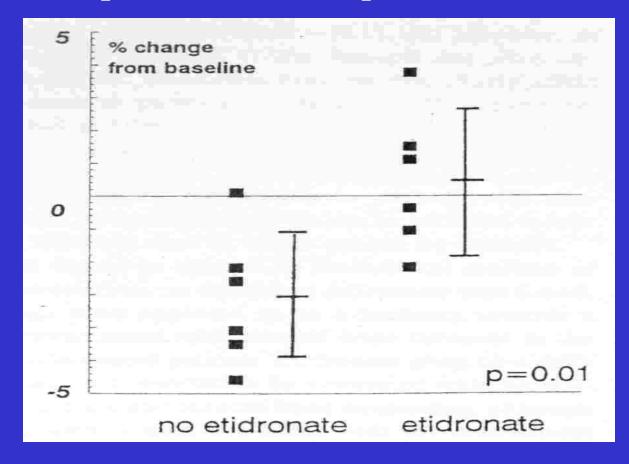
- Less pruritus
- A greater fall in enzymes and IgM
- Less histological disease activity
- Less progression of the histological stage

PBC: Prednisone + AzathioprineWolfhagen FH(J Hepatol 1998; 29:736-42)Pred + Aza + UDCA: dotted lineUDCA alone: solid line



PBC Bone Loss: Etidronate (400 mg/day 2 of 11 weeks)

WolfhagenJ Hepatol 1997;26:325-301 year RCT.All patients received prednisone (~10 mg/day)



Conclusion

- Despite significant effects on some mainly biochemical – variables, UDCA has no significant beneficial effect on symptoms, mortality or the need for liver transplantation.
- Other effective (immunosuppressive) therapies (including azathioprine and glucocorticosteroids) should not be withheld from the patients.
- However, more effective therapies are needed.
- Better understanding of the etiology is important.
- Gene-technology may be a valuable tool.