PSC Partners Seeking A Cure

2010 Conference Agenda

In Conjunction with The Liver Center at Yale School of Medicine

The Natural Course of PSC: Treatment and Managing Symptoms

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PSC is a Rare Disease (i.e., <200,000 affected patients)

Region (Author) Publication	Time interval	Population	Number of cases of PSC	Incidence (per 100,000/year)	Prevalence (per 100,000)
Olmsted County, MN (Bambha et al.) Gastroenterology 2003	1976–2000	NA	22	0.9	13.6

NA, not available

Estimated total affected US patients: 41,752 (1 in ~ 7,300)

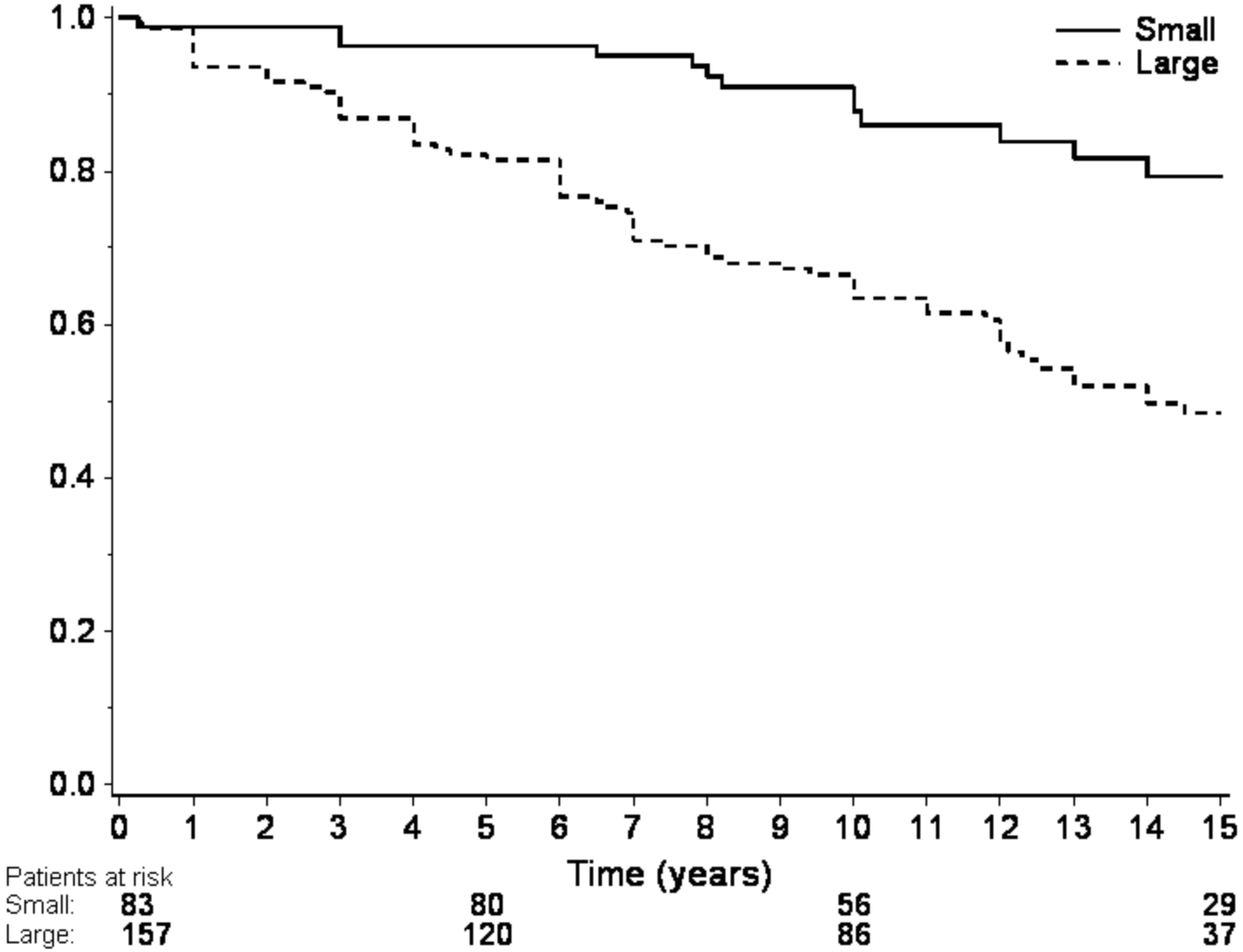
Transplants for PSC: ~200/year, i.e., 0.06 per 100,000/yr

Office of Rare Diseases Research
National Institutes of Health

PSC is highly heterogeneous

- Large duct PSC
- Small duct PSC
- PSC - AIH overlap
- IgG4 positive PSC and AIP

Survival of small-vs.large duct PSC



Natural history determined by presence/absence of symptoms: Asymptomatic patients have non-progressive or slowly progressive disease

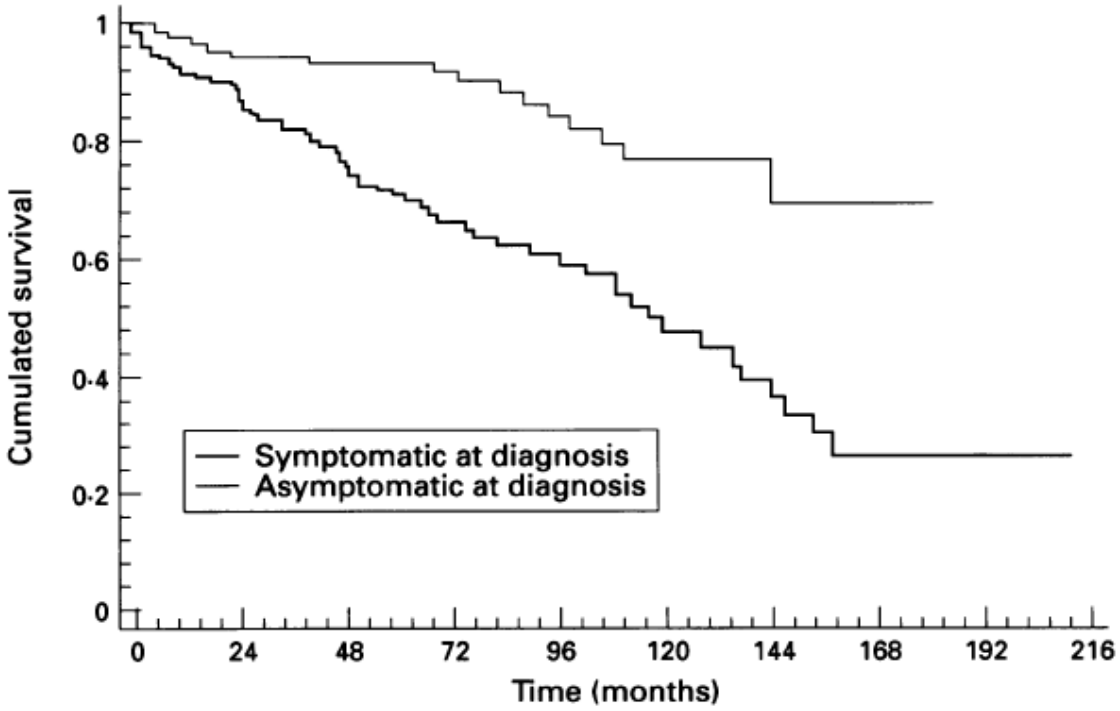
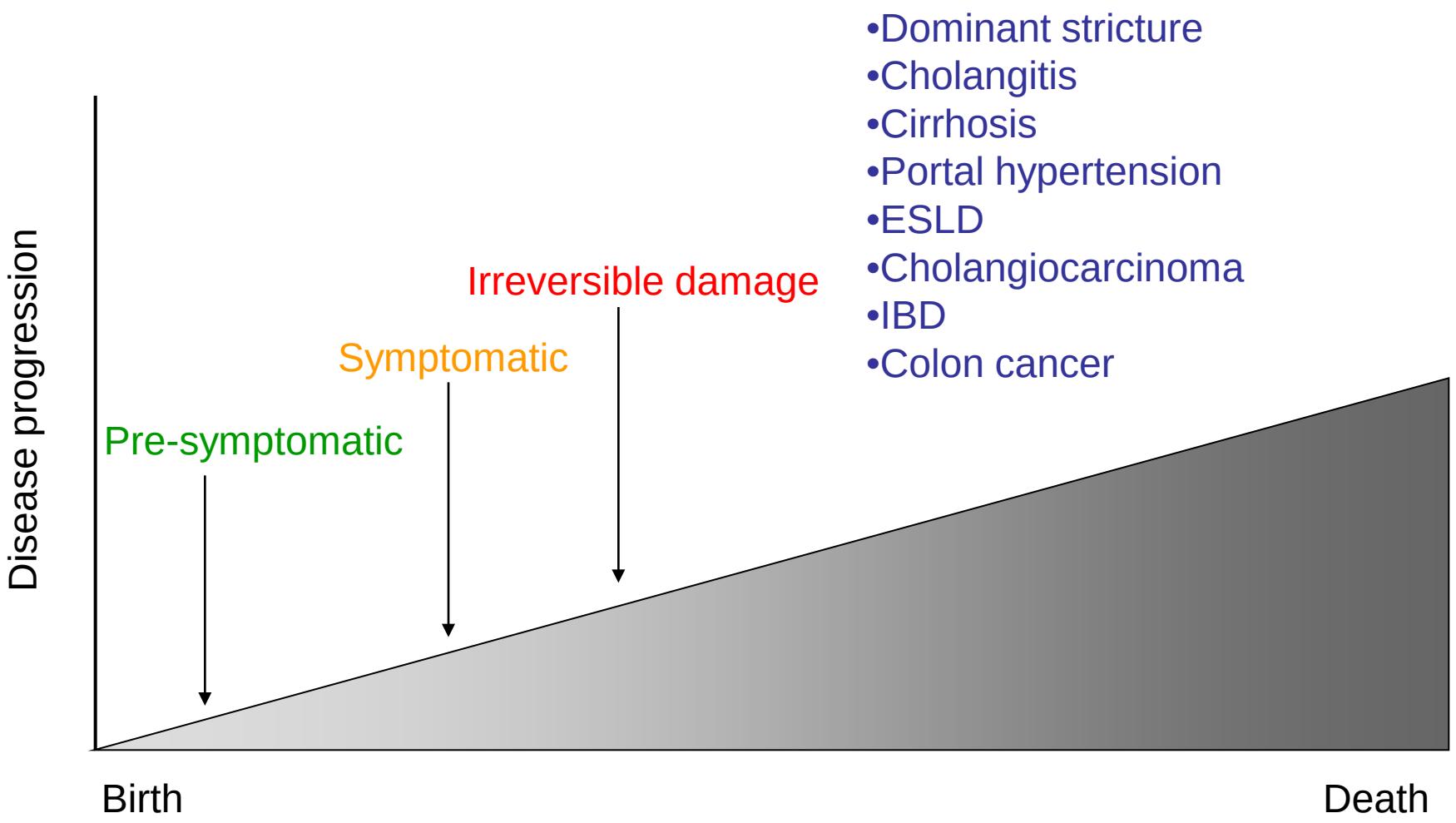


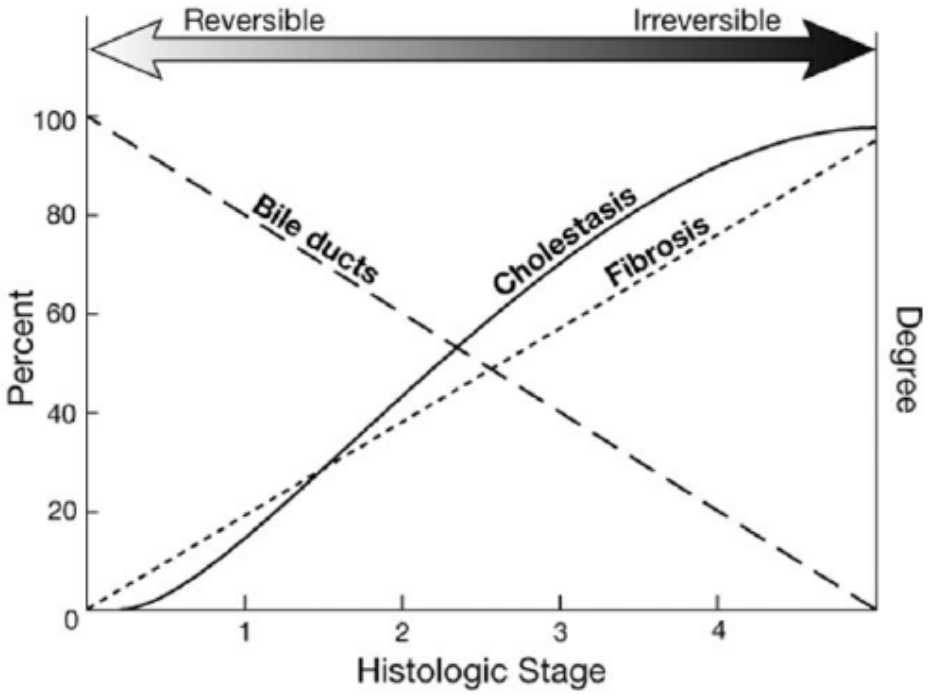
Figure 1: Kaplan-Meier estimated survival curves of symptomatic and asymptomatic PSC patients ($p<0·001$).

Helzberg, H, Petersen JM and Boyer JL, 1987
Broome et al, 1996

PSC modeled as a **chronic progressive** disease



Natural History of PSC



Lindor K, et al, 2006

PSC Progresses at *Variable* Rates to Biliary Cirrhosis

Table 2. Prognostic Models in PSC: Factors

Reference (year)	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Wiesner[2] (1989)	Age	Bilirubin	Histology	Hemoglobin	IBD
Farrant[25] (1991)	Age	Alkaline Phosphatase	Histology	Splenomegaly	Hepatomegaly
Dickson[26] (1992)	Age	Bilirubin	Histology	Splenomegaly	
Broome[27] (1996)	Age	Bilirubin	Histology		
Okolicanyi[28] (1996)		Cholesterol	ALT		
Kim[29] (2000)	Age	Bilirubin	AST	Albumin	Variceal Bleeding

Abbreviations: Alk Phos, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IBD, inflammatory bowel disease.

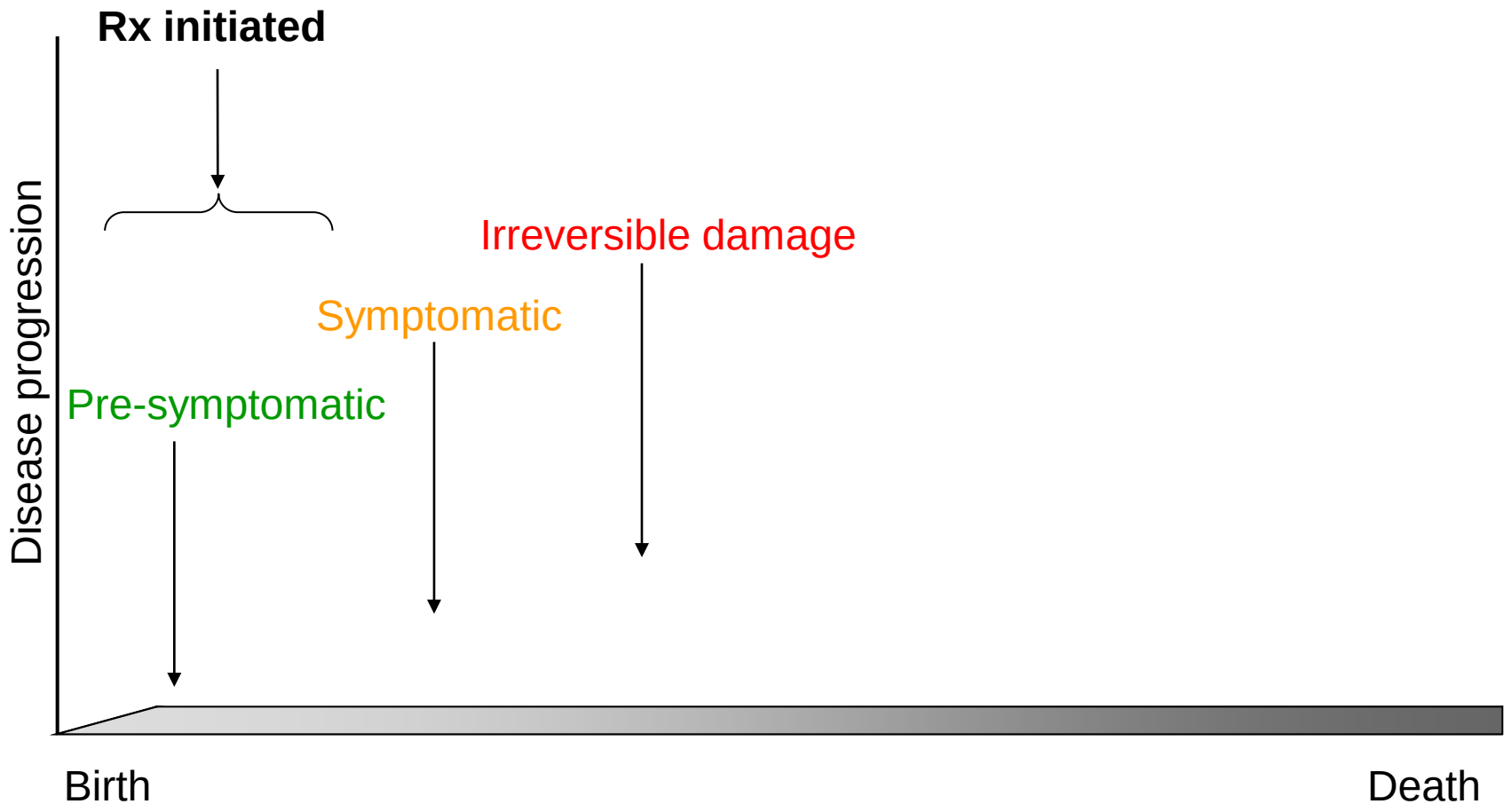
Median ‘survival’ (time to transplant) after diagnosis: 10-12 yrs

Natural history is highly variable
Not possible to predict individual patient prognosis

Therapeutic Goals

- Cure PSC
- Improve QoL: relieve symptoms
- Prevent disease progression
- Prevent hepatobiliary cancer
- Prevent colon cancer in PSC/IBD

Prevention based on **early intervention**



Ten steps on an ideal journey

1. Assemble your team
2. Hepatologist
3. Gastroenterologist
4. Primary care physician
5. Time to talk about implications of results
6. Regular review with a ‘strategic perspective – ‘looking beyond the next appointment’
7. Understand disease trajectory
8. Care of associated medical conditions
9. Participate in research studies
10. Become an advocate: ‘*PSCer*’

Physician's approach to PSC

- Be optimistic
- Be problem oriented
- Be cautious
- Collaborate
- Be available
- Provide confidence through information

Managing PSC

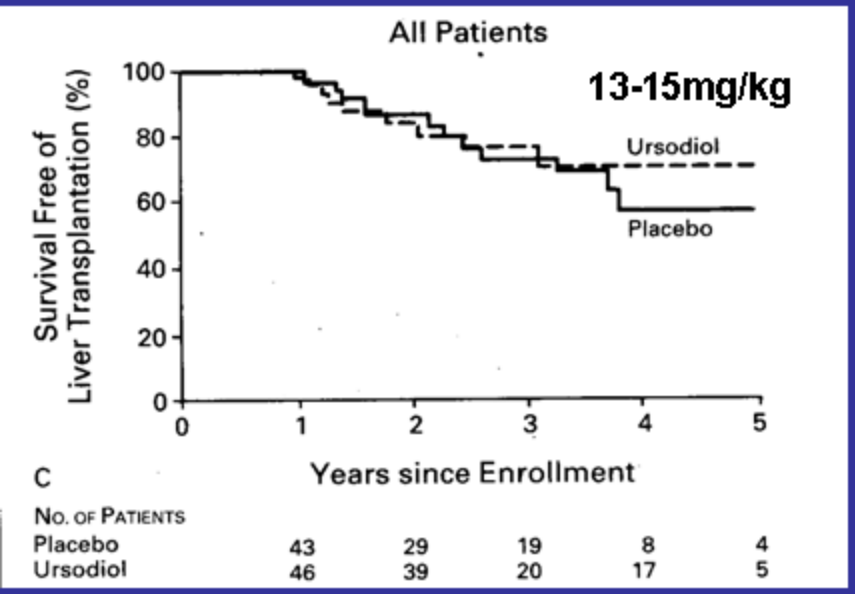
- Dominant strictures
- Cholangitis
- Pruritus
- Portal hypertension
- Metabolic bone disease
- IBD
- Cancer surveillance: CCC, gallbladder, colon
- Optimal timing of liver transplantation when indicated

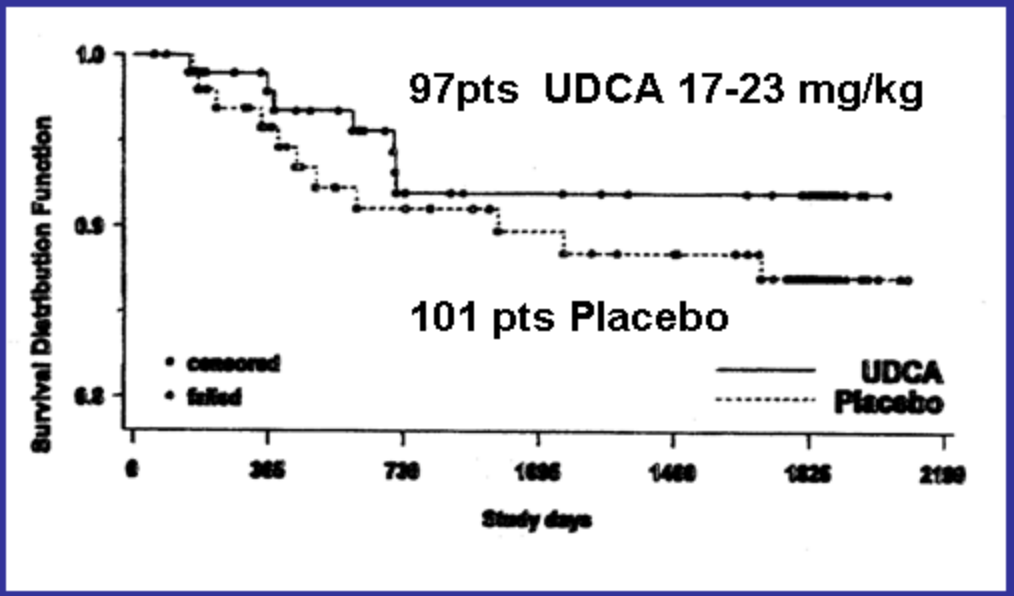
Medical Therapy: Past disappointments

- Steroids
- Azathioprine
- Cyclosporine, Tacrolimus
- Methotrexate
- antiTNF
- Colchicine
- Sylimarin

What about UDCA?

Low dose UDCA*vs Mod dose in PSC**
Survival Free of Liver Transplantation



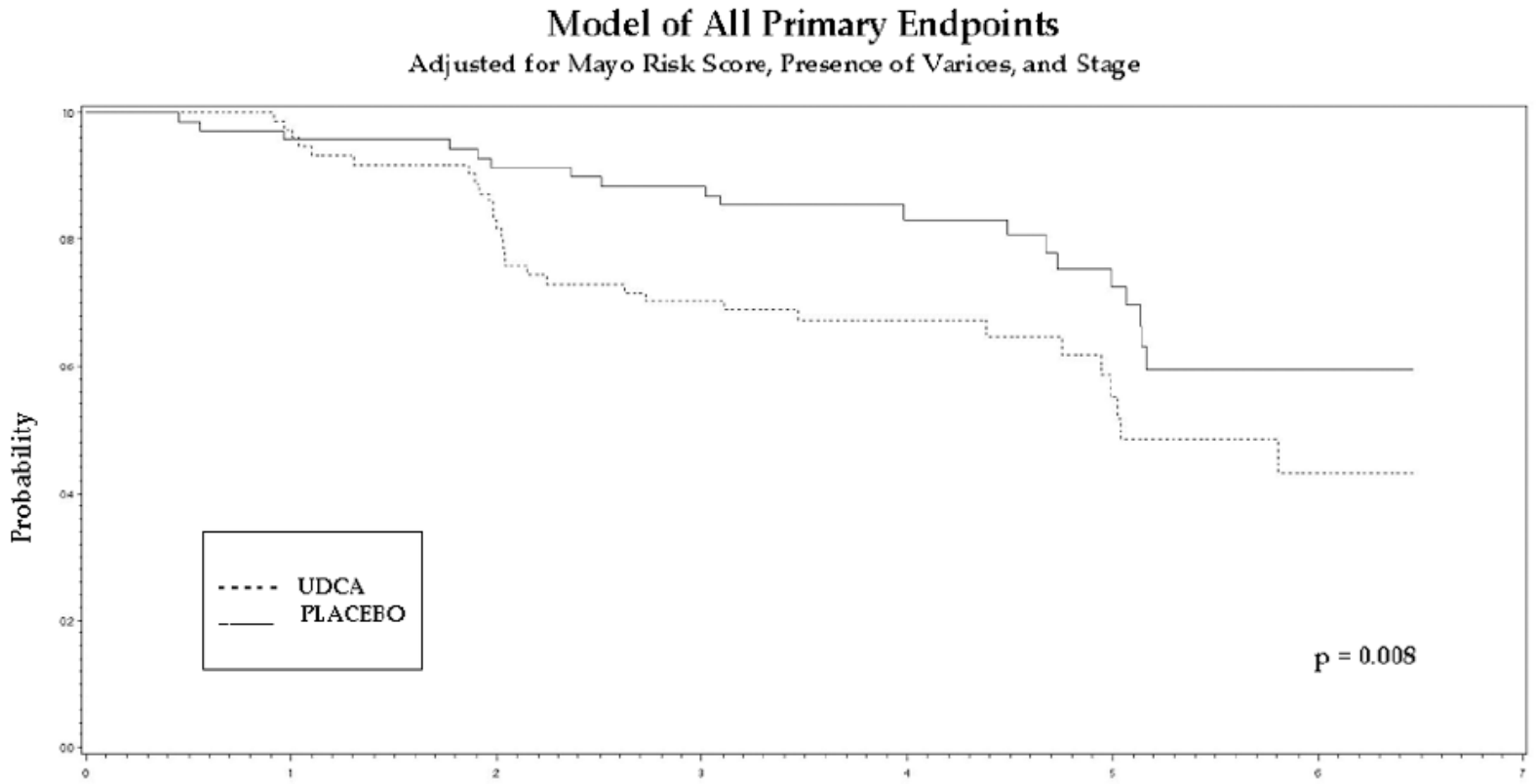


*Lindor et al;N Engl J Med 1997

**Olsson et al;J Hepatol 2004

Death /Transplantation:
7.2% UDCA vs 10.9% placebo (ns)

High Dose UCDA Trial



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

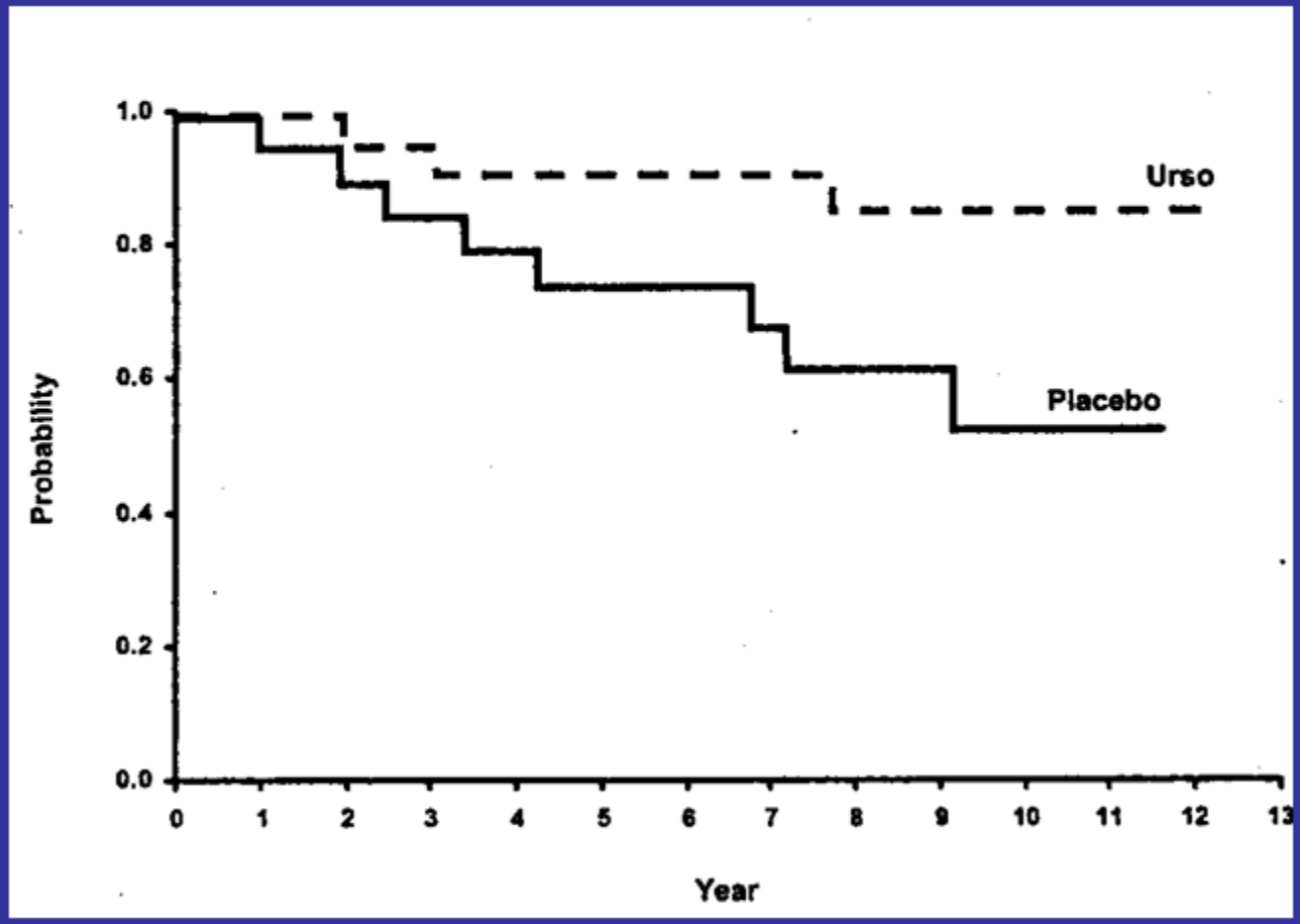
Lindor et al, 2009

UCDA in PSC: Conclusion

- High dose 25-30 mg/kg not indicated ? Toxic level of UDCA
- Lower doses safe but / efficacy to alter natural history
- AASLD guideline 2010: ‘stop UCDA’

Alternative approach: invidualize UDCA therapy

Proportion of PSC/UC pts free of colonic cancer / dysplasia*



n=29

n=23

*Pardi et al,Gastro 2003;124:889-3

New Bile Acids
Nor-UCDA, c23 Homolog of UDCA

- Biliary enrichment with hydrophillic norUDCA
- Bicarbonate-rich choleresis
- Induction of alternative bile acid detoxification
- Direct anti-inflammatory and anti-fibrotic properties

ATTRACTIVE CANDIDATE FOR TREATMENT OF PSC

Nor-UDCA

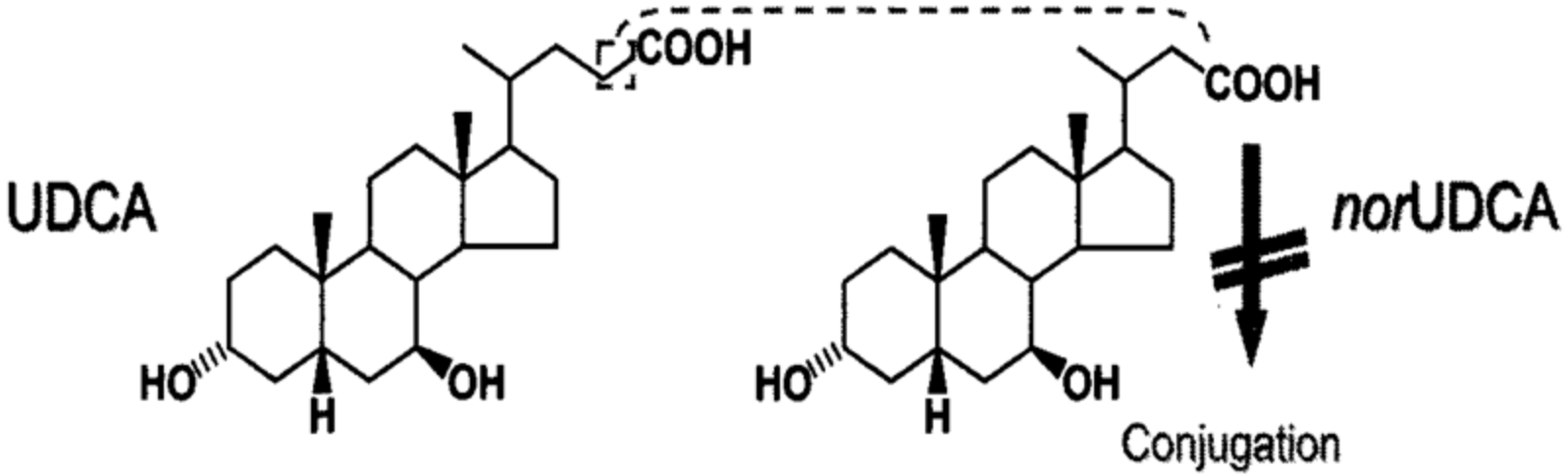


Figure 2 Chemical structure of *nor*UDCA and UDCA. *nor*UDCA (right) is a side chain-shortened C_{23} homologue of UDCA (left) and possesses one less methylene group in its side chain (dotted box), conferring relative resistance to amide conjugation

GASTROENTEROLOGY 2006;130:465–481

24-*nor*Ursodeoxycholic Acid Is Superior to Ursodeoxycholic Acid in the Treatment of Sclerosing Cholangitis in *Mdr2 (Abcb4)* Knockout Mice

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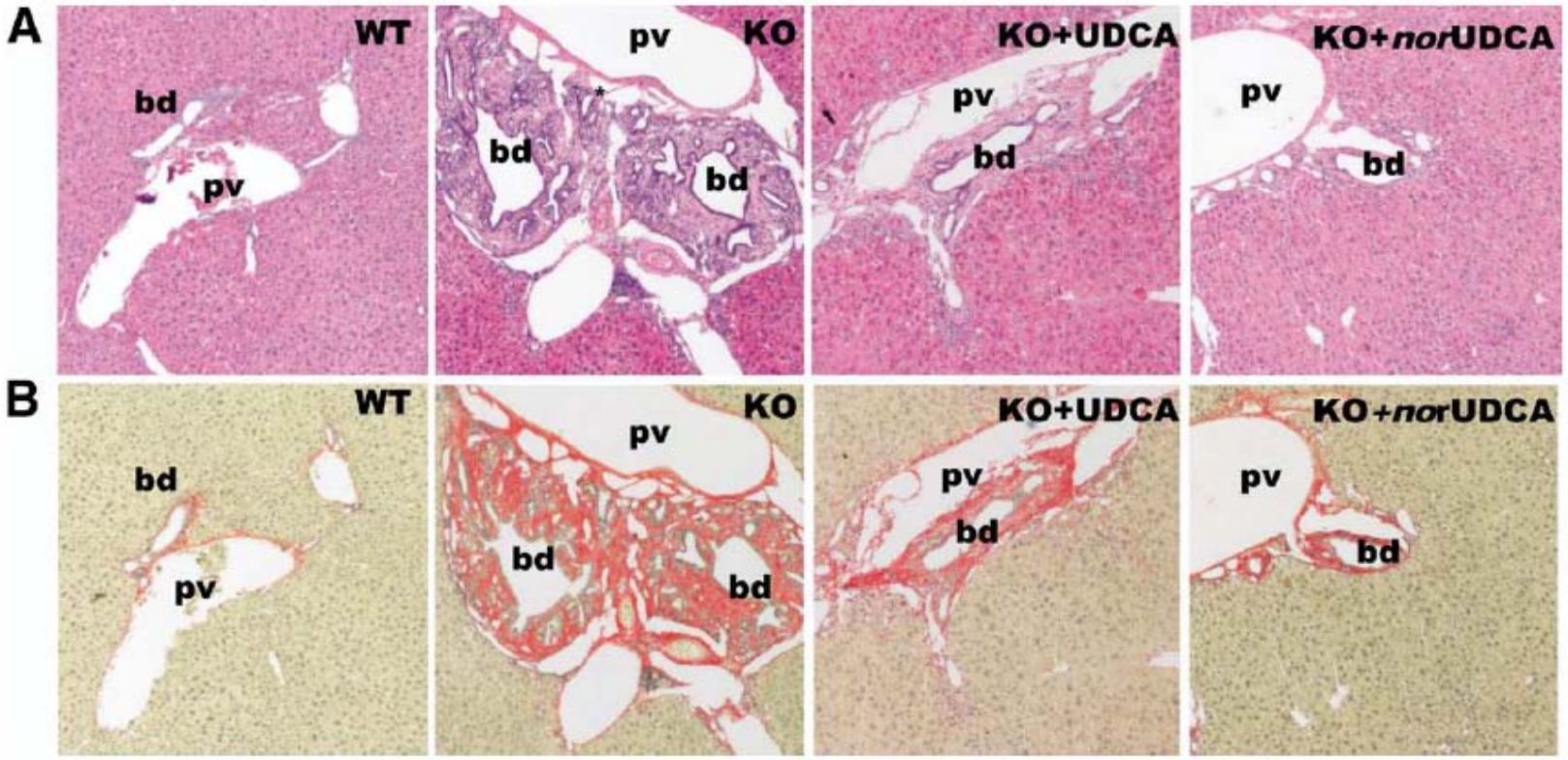
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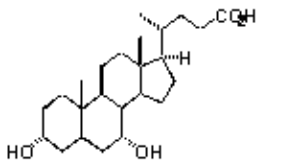
Farsenoid X Receptor (FXR): the Endogenous Bile Acid Sensor

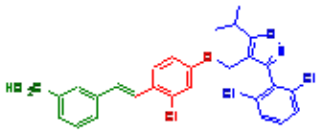
FXR

Nuclear receptor expressed in liver, intestine, kidney, adrenal glands



CDCA (primary bile acid)

- Discovery: FXR - bile acid receptor: CDCA natural ligand (1999)



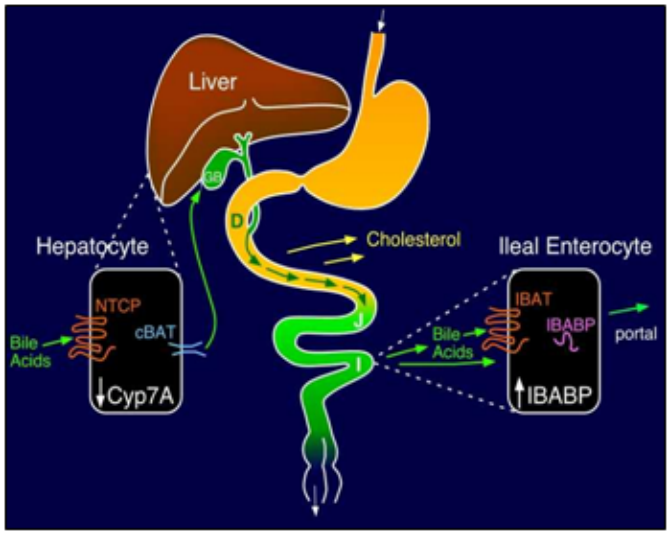
GW4064

- Potent FXR agonist as a chemical tool compound developed (2000)

CYP7A1, SHP, BSEP, MRP2, MDR3, I-BABP

- Hepatocyte FXR target genes identified (2000)

- **FXR role in bile flow and biosynthesis regulation (2001)**



EASL Single Topic Conference Trauner M, 2006

INT-747: First-in-class FXR Agonist

- INT-747 is 6α-ethyl-chenodeoxycholic acid (6-ECDCA) with generic name obeticholic acid
- Semi-synthetic derivative of CDCA
- Potent FXR agonist
  - UDCA : no FXR-mediated effects
  - INT-747: ~100x more potent FXR agonist than CDCA
  - INT-747 is a selective FXR agonist

Potential Indications for FXR Drugs

Liver and biliary tract

Cholestatic disorders

- *Primary biliary cirrhosis (PBC)*
- *Primary sclerosing cholangitis (PSC)*
- Intrahepatic cholestasis of pregnancy
- Biliary atresia

Fibrosis associated with:

- Nonalcoholic fatty liver disease (NAFLD)/ nonalcoholic steatohepatitis (NASH)
- Chronic viral hepatitis (HBV & HCV)
- Alcoholic liver disease
- Autoimmune hepatitis

Liver transplantation

Cholesterol gallstone disease

Intestinal

Bacterial overgrowth

Inflammatory bowel diseases (IBD)

Colon cancer

Metabolic diseases

Dyslipidemia

Atherosclerosis

Diabetes

Kidney diseases

Diabetic nephropathy

Renal fibrosis

Rifampicin

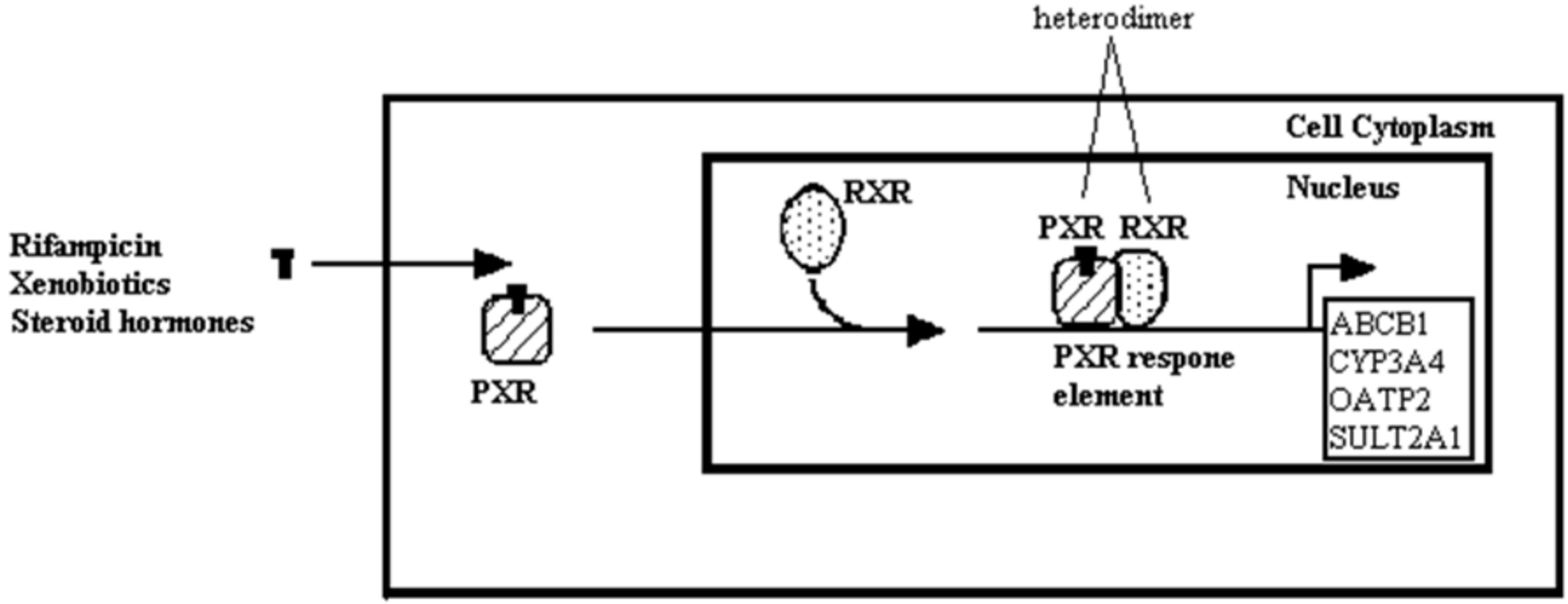
- Potent antibiotic
- Antipruritic agent
- Potent inducer of PXR:

  - *potential benefits in cholestasis*

- NB idiosyncratic hepatitis in PBC

Rifampicin- potent inducer of PXR

Fig 6. Inducers of PXR such as rifampicin stimulate the intracellular proteins to forms heterodimers (e.g pregnane x receptor PXR with the retinoid x receptor RXR). This heterodimer then binds to DNA recognition motifs and induces transcription of the gene, therefore coordinately upregulating a number of ABC transporters such as ABCB1 (MDR1), OATP2, SULT2A1 and the enzyme CYP3A4.



Conclusion : Further Studies required?

Long term antibiotics in PSC*

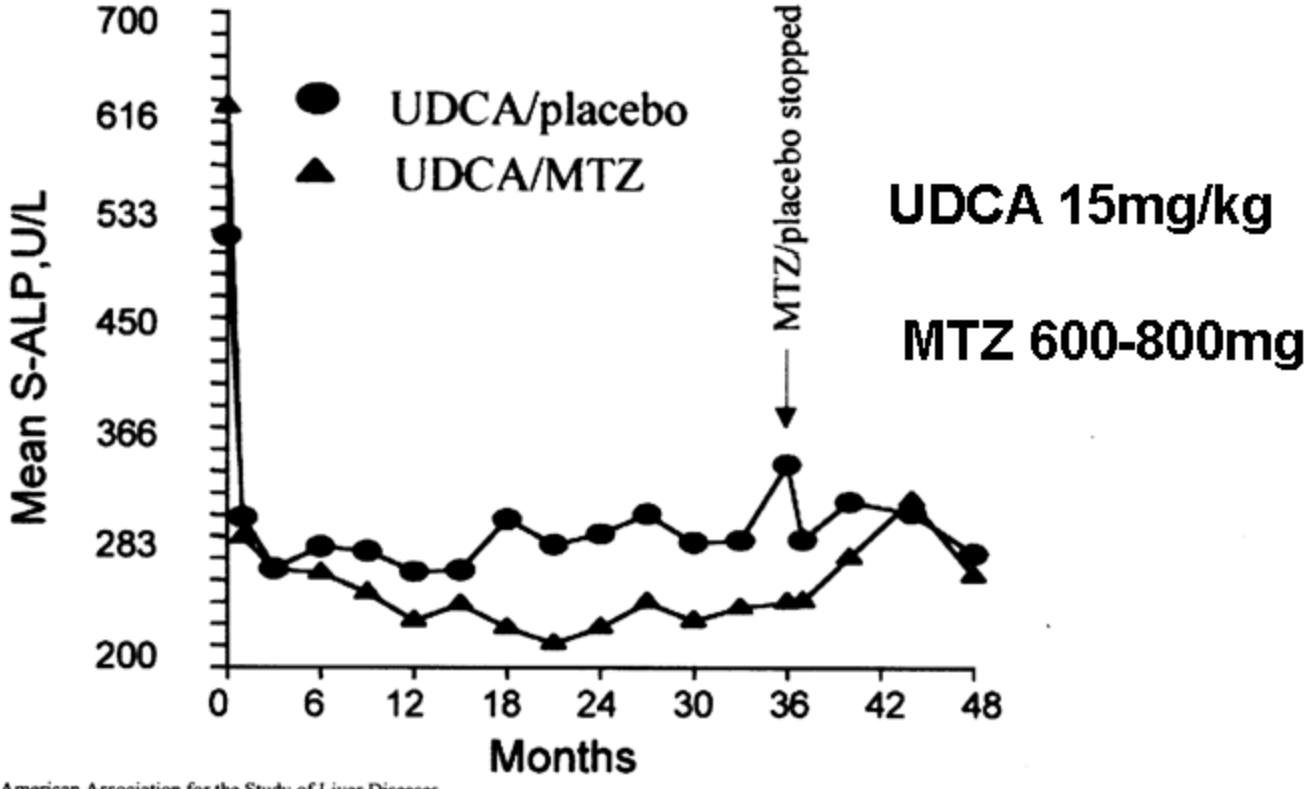


Figure 1. The effect of UDCA/placebo or UDCA/MTZ on mean serum ALP levels during 36 months.

*Farkkila et al ;Hepatology 2004;40:1379

Effect of therapy on Liver Histology (Stage& Grade) during 3 years follow up*

Change in histology	UDCA + placebo (n=36)	UDCA + MTZ (n=32)
Stage , n(%)		
Improvement	5 (14%)	11 (34%) p<.047
No change	20 (56%)	9 (28%) p<.022
Worsening	11 (30%)	12 (38%) ns
Grade ,n(%)		
Improvement	6 (17%)	14 (44%) p< .014
No change	15 (42%)	9 (28%) ns
Worsening	15 (41%)	9 (28%) ns

*Farkkila et al;2004

Treatment of PSC: Future Prospects

- New bile acids
- Nuclear receptor agonists
- Biologics: Adhesion molecule blockers
- Long term antibiotics

Delineation of genetic pathophysiology will lead to new therapeutic targets

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Thank You!