Que Faire quand l'AUDC ne Suffit Pas ? Aujourd'hui

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Paris, Mai 2016

Résistance à l'AUDC (critères de Paris): Causes

- **En général:**
  - **Cirrhose ou ductopénie sévères**
  - **Overlap syndrome CBP – HAI* (importance de la PBH)**
  - **Mauvaise observance* (interrogatoire, dosage AUDC)**

- **Beaucoup plus rarement:**
  - **Dysthyroidie***
  - **Maladie coeliaque***
  - **Autres* : intoxication à la vitamine A, fistule artério-veineuse post-PBH, PAL d'origine osseuse…**

(*: causes éventuellement corrigeables)

Interrogatoire, Biologie, Echographie, Biopsie hépatique +++

Diagnostic d'Overlap: Propositions Pratiques

Présence d'au moins 2 des critères habituels de chacune des 2 maladies :

- **HAI**
  - **ALAT > 5 N**
  - **IgG > 2N ou anti-muscle lisse (AML) ≥ 1/40**
  - **Nécrose parcellaire lymphocytaire d'intensité moyenne ou sévère (critère indispensable)** → **PBH**
- **CBP**
  - **PAL > 2 N ou GGT > 5 N**
  - **Anticorps anti-mitochondries (AMIT) ≥ 1/40**
  - **Lésions florides des canaux biliaires interlobulaires**

(EASL Guidelines, J Hepatol 2009)

Overlap: Traitement

- **Combinaison corticoïdes – AUDC: recommandée**
  dose initiale predniso(lo)ne 0,5 mg/kg/j ou
  budesonide 9mg/j [en l'absence de cirrhose]
  +/- azathioprine (III/C2)

OU

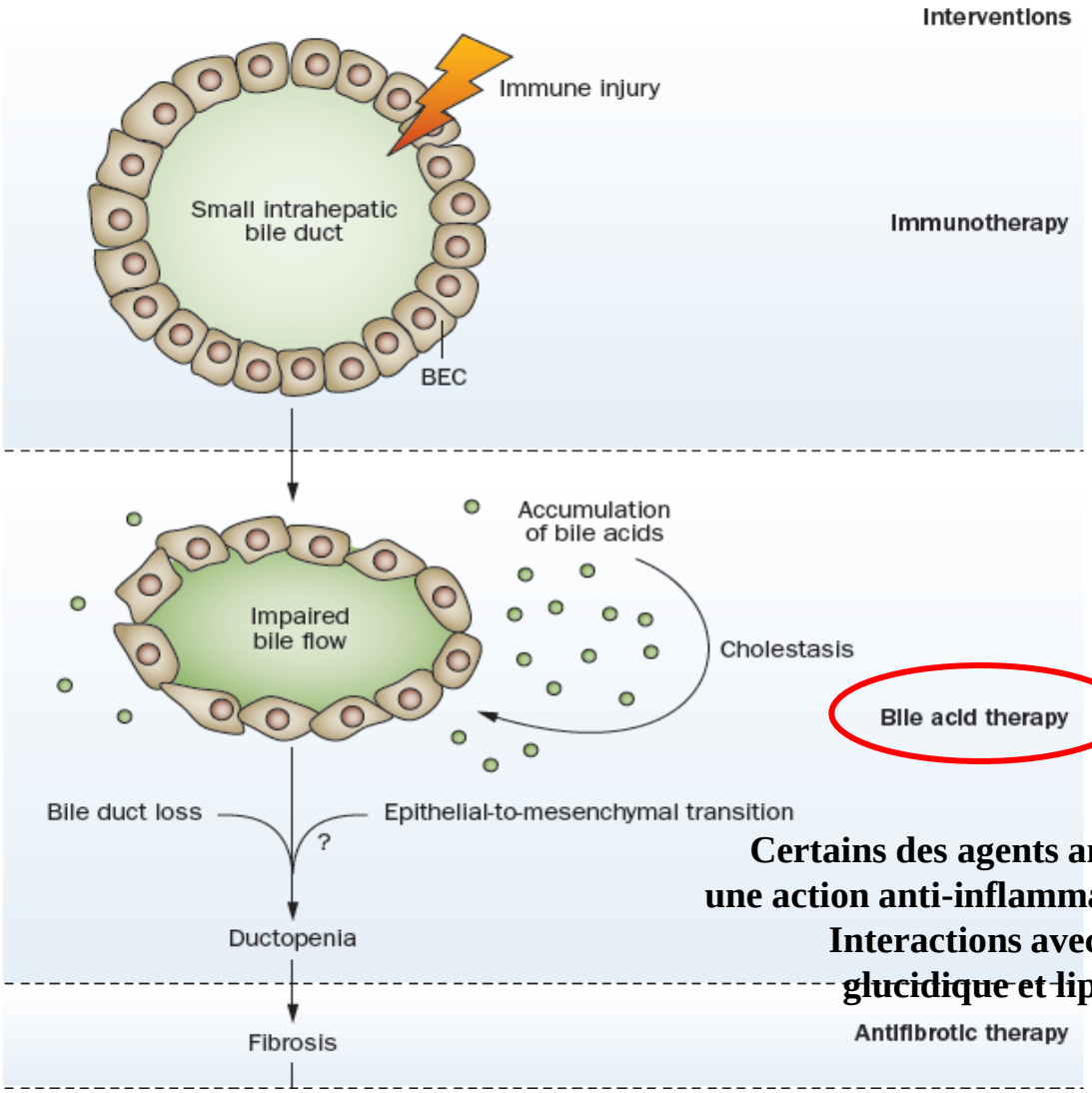
- **Commencer par AUDC seul et n'ajouter stéroïdes qu'en l'absence de réponse biochimique à 3 mois (III/C2)**

(EASL Guidelines, J Hepatol 2009)

Résistance sans Overlap ni Autre Cause « Corrigeable » Identifiée

Aucun traitement adjuvant validé mais…

(Dyson et al, Nat Rev Gastroenterol Hepatol 2015)

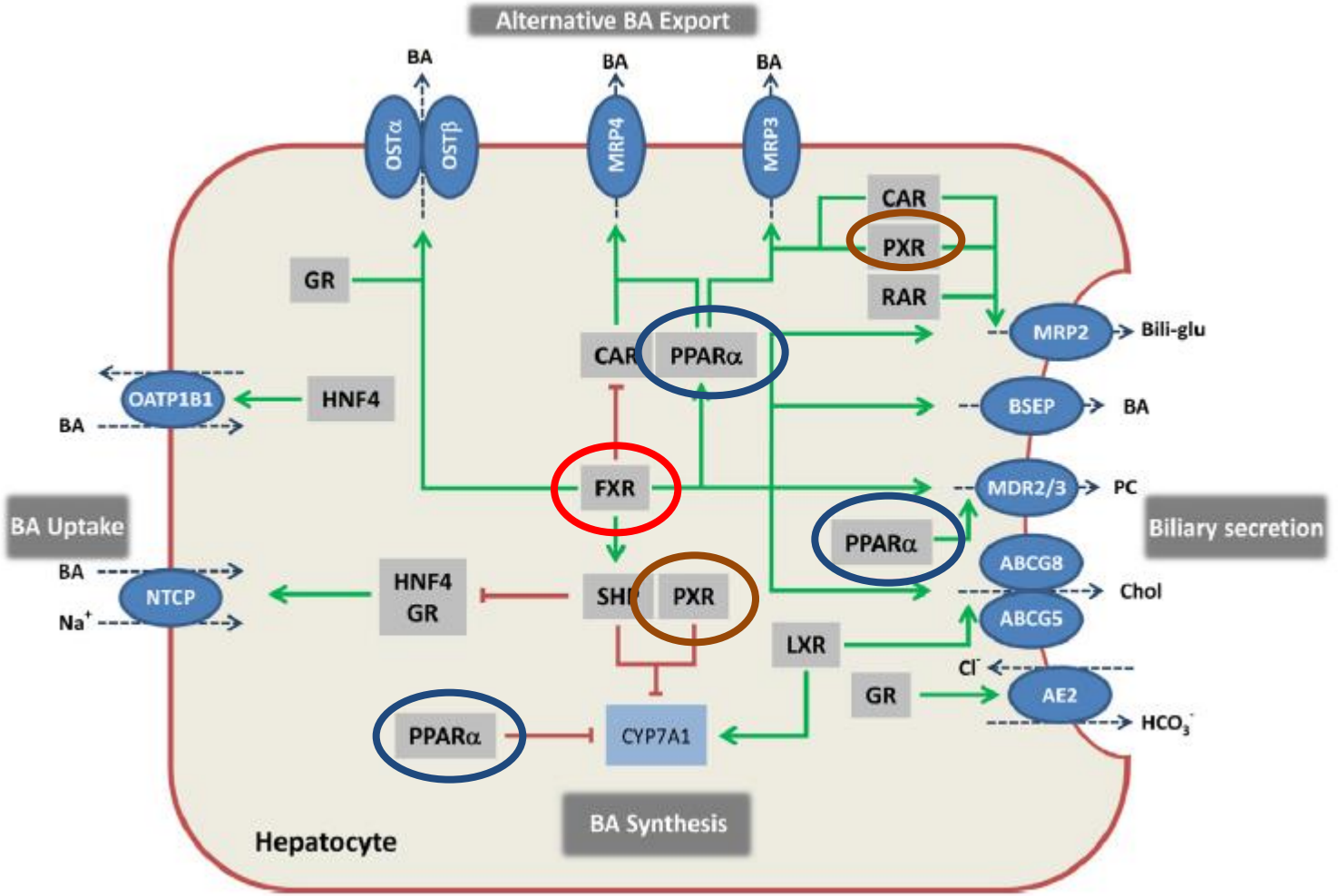


Certains des agents anti-cholestatiques ont une action anti-inflammatoire et anti-fibrosante. Interactions avec le métabolisme glucidique et lipidique (NASH)

« Nouveaux » Agents Anti-Cholestatiques

- ***nor*UDCA**
- **Acide Obeticholique (agoniste FXR)**
- **Fibrates (agoniste PPAR)**
- **Budesonide**
- **Autres: Agonistes FGFR4 (analogue FGF19), Inhibiteurs ASBT**

Transcriptional Regulation of Hepatocellular Bile Regulation



(Halilbasic et al, J Hepatol 2013)

Budesonide (1)

- **Prednisolone (30 puis 10mg/j):**
  - **essai randomisé vs placebo (19/17) sur 3 ans**
  - **↓S PAL et Ig, ↓NS progression vers cirrhose**
  - **Mais: effets secondaires ++ (diabète, os, poids…)**

(Mitchison et al, J Hepatol 1992)

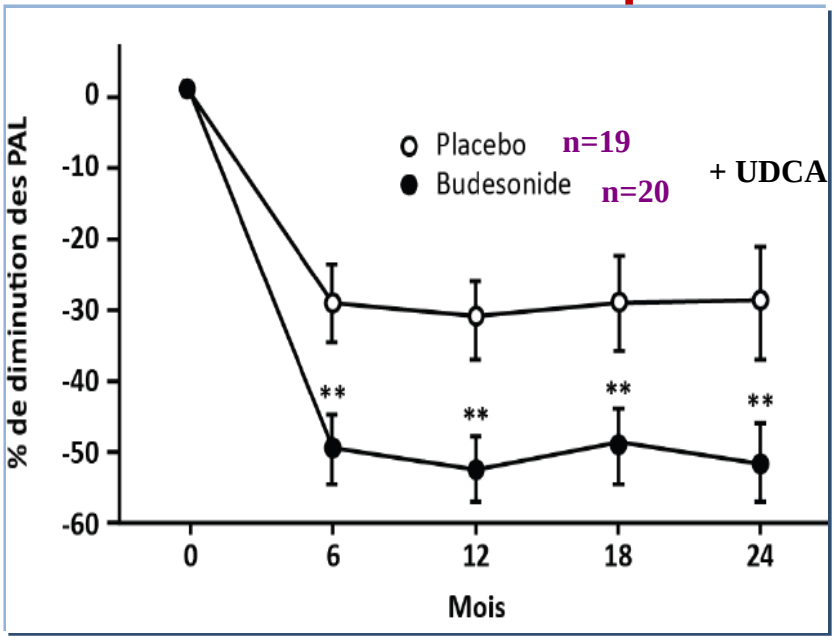
- **Interêt potentiel du Budesonide:**
  - **Agoniste du glucocorticoid receptor (affinité x 15-20 vs prednisolone) avec forte extraction hépatique**
  - **Agoniste PXR**
  - **Mais contre-indiqué en cas de CBP au stade de cirrhose sévère (pharmacocinétique modifiée, thrombose porte (2/7)?)**

(Hempflinget al, Hepatology 2003)

AUDC + Budesonide [9mg/j] (1)

Essai randomisé:

CBP « naïves » à un stade précoce



(Leuschner et al, Gastroenterology 1999)

Densité osseuse: pas de baisse significative

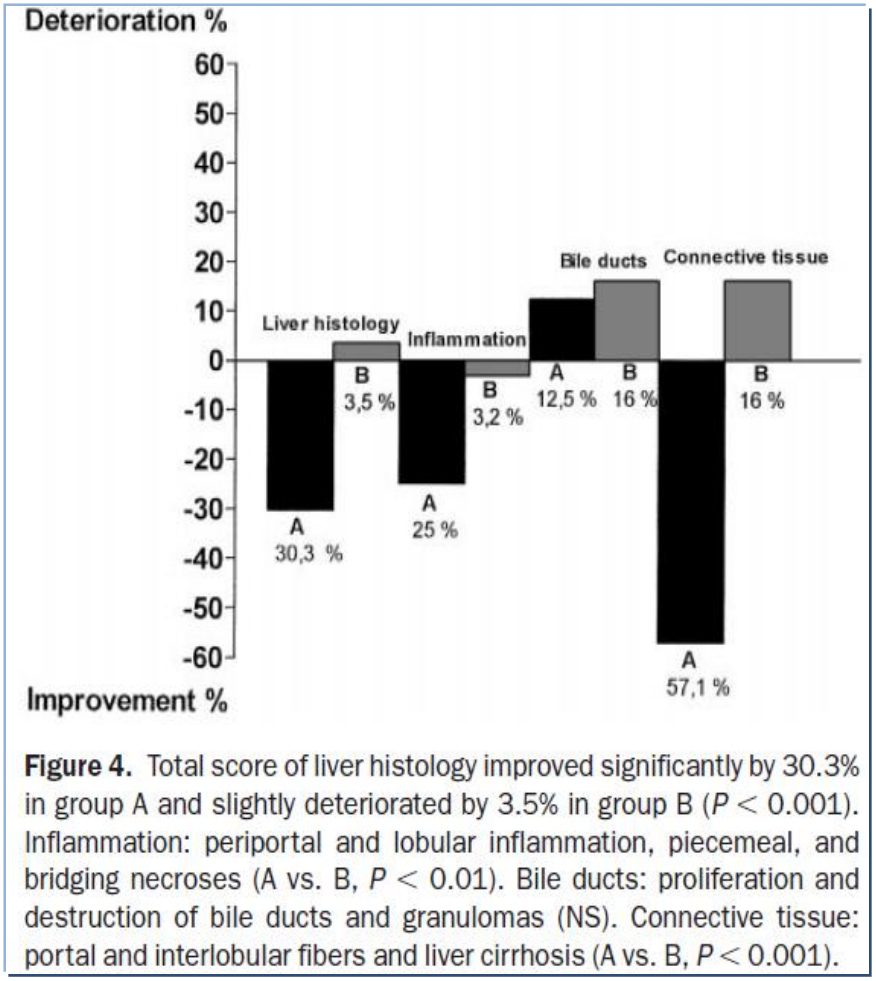
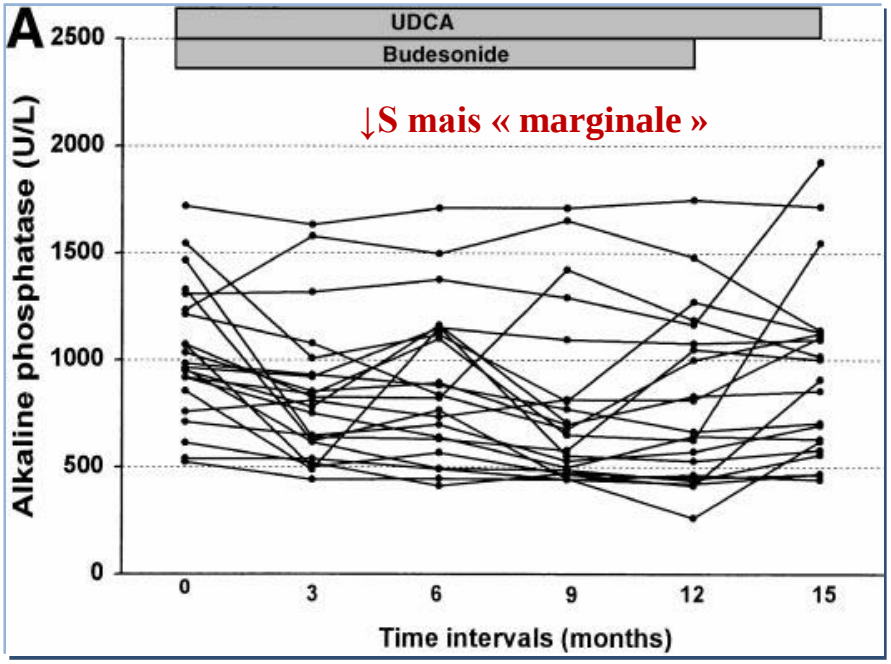


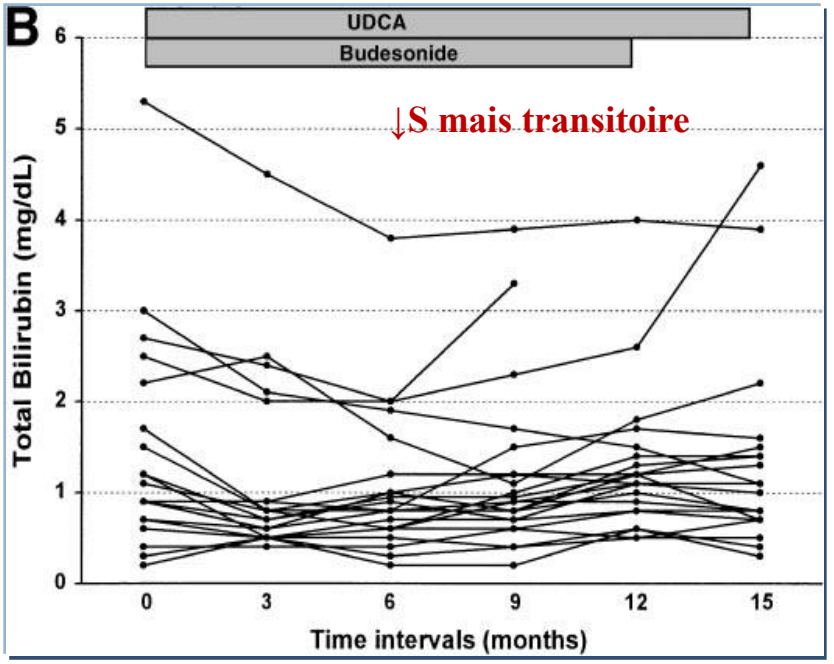
Figure 4. Total score of liver histology improved significantly by 30.3% in group A and slightly deteriorated by 3.5% in group B ($P < 0.001$). Inflammation: periportal and lobular inflammation, piecemeal, and bridging necroses (A vs. B, $P < 0.01$). Bile ducts: proliferation and destruction of bile ducts and granulomas (NS). Connective tissue: portal and interlobular fibers and liver cirrhosis (A vs. B, $P < 0.001$).

AUDC + Budesonide [9mg/j] (2)

- **Etude pilote: 22 CBP avec PAL ≥ 2N sous AUDC (stade histologique ?)**

(Angulo et al, Hepatology 2000)



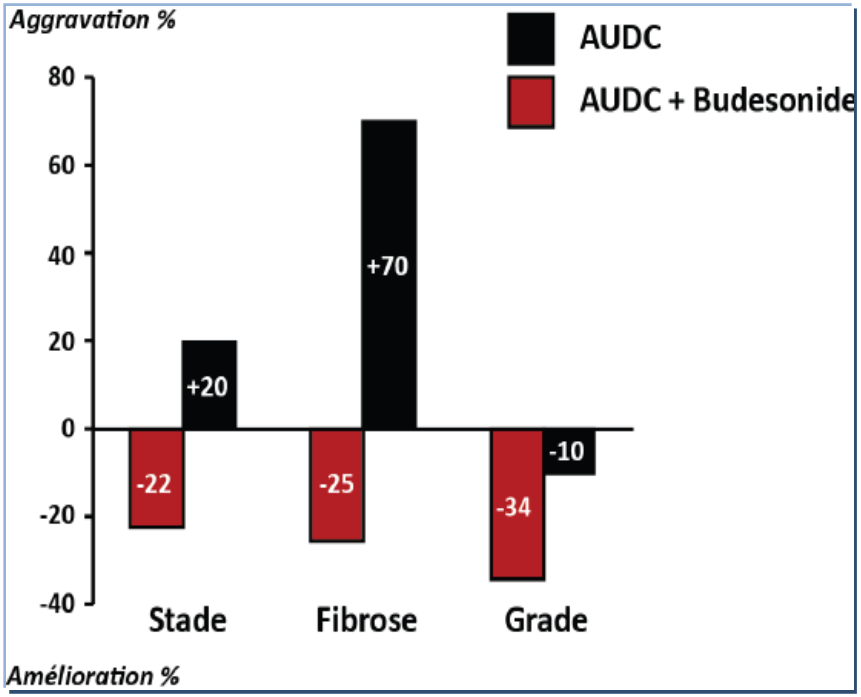


- **↓S DMO**
- **Conclusions:** The results of this pilot study would seem to discourage further controlled trials of budesonide…

AUDC + Budesonide [6mg/j] (3)

- **Etude randomisée (mais sans placebo): 77 CBP « naïves » non cirrhotiques, 3 ans**

(Rautianen et al, Hepatology 2005)



- **↓S: PAL, GGT, ALT, Ig**
- **7/37: effets sec. modérés (pas de DMO systématique)**

- **Résultats en attente d'une grande phase III randomisée pdt 3 ans (AUDC + Bude vs AUDC + Place) : 183 CBP non cirrhotiques (2/1)**
  - **Critère principal: histologie (fibrose stable ou ↓ et ↓ inflammation)**
  - **Début: 2008, arrêt des inclusions: 2014…**

AUDC + Budesonide [6mg/j] (+ MMF 1,5 g/j) (4) Expérience de Saint Antoine

- **17 CBP non cirrhotiques, non répondeuses à l'AUDC (Paris 1) et avec hépatite d'interface ≥ A2 suivies 3 ans**

Table 2 Clinical and biochemical response to combined therapy in the entire cohort.

	At enrollment	At last visit	*p*
Pruritus	12 (80%)	1 (16%)	0.05
Total bilirubin	19 (12–32)	12 (8–15)	0.06
Albumin	38 (35–44)	38 (39–46)	0.70
Prothrombin index	100 (90–105)	100 (95–102)	0.58
Platelets	250 (211–313)	238 (191–303)	0.13
AST	92 (49–132)	39 (35–70)	< 0.0001
ALT	118 (70–210)	44 (30–73)	< 0.0001
Alkaline phosphatase	380 (241–566)	168 (115–280)	< 0.0001
Hyaluronic acid	54 (31–87)	52 (27–88)	0.08
IgG	15 (13–20)	12 (9–15)	0.001
IgA	1.8 (1.0–2.7)	1.7 (1.0–2.6)	0.05
IgM	4.9 (2.4–8.1)	2.7 (1.3–3.9)	< 0.0001

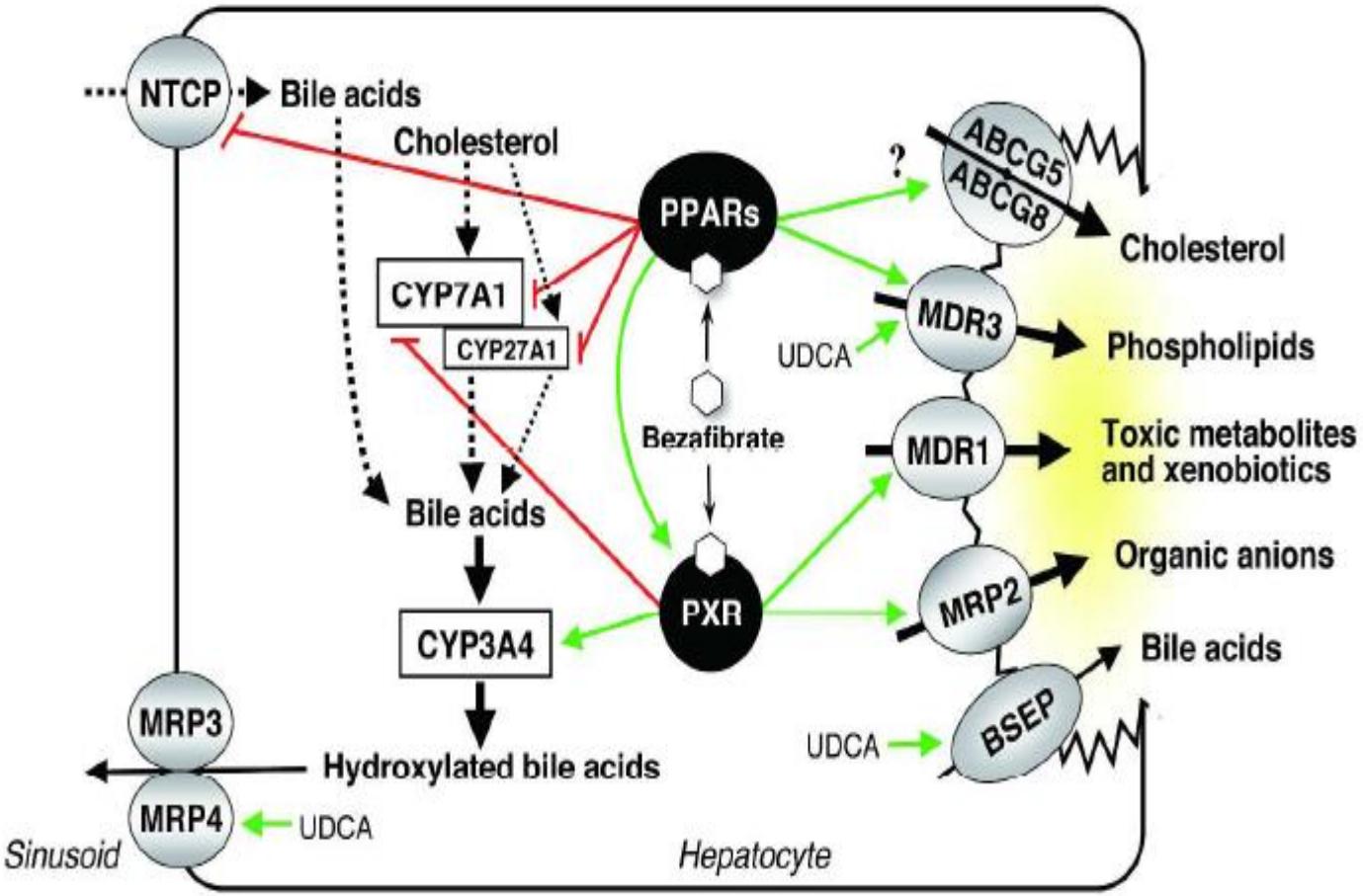
Table 3 Histological activity and fibrosis grades in the initial (at enrollment) and the final liver biopsy.

	Initial	Final	*p*
Activity			
A0-A1	0 (0%)	12 (80%)	0.002
A2	12 (80%)	3(20%)	
A3	3 (20%)	0(10%)	
Fibrosis			
F0-F1	3 (20%)	9 (60%)	0.03
F2	8 (53%)	4 (27%)	
F3	4 (27%)	2 (13%)	

(Rabahi et al, Gastroenterol Clin Biol 2010)

- **Absence d'effets secondaires significatifs**

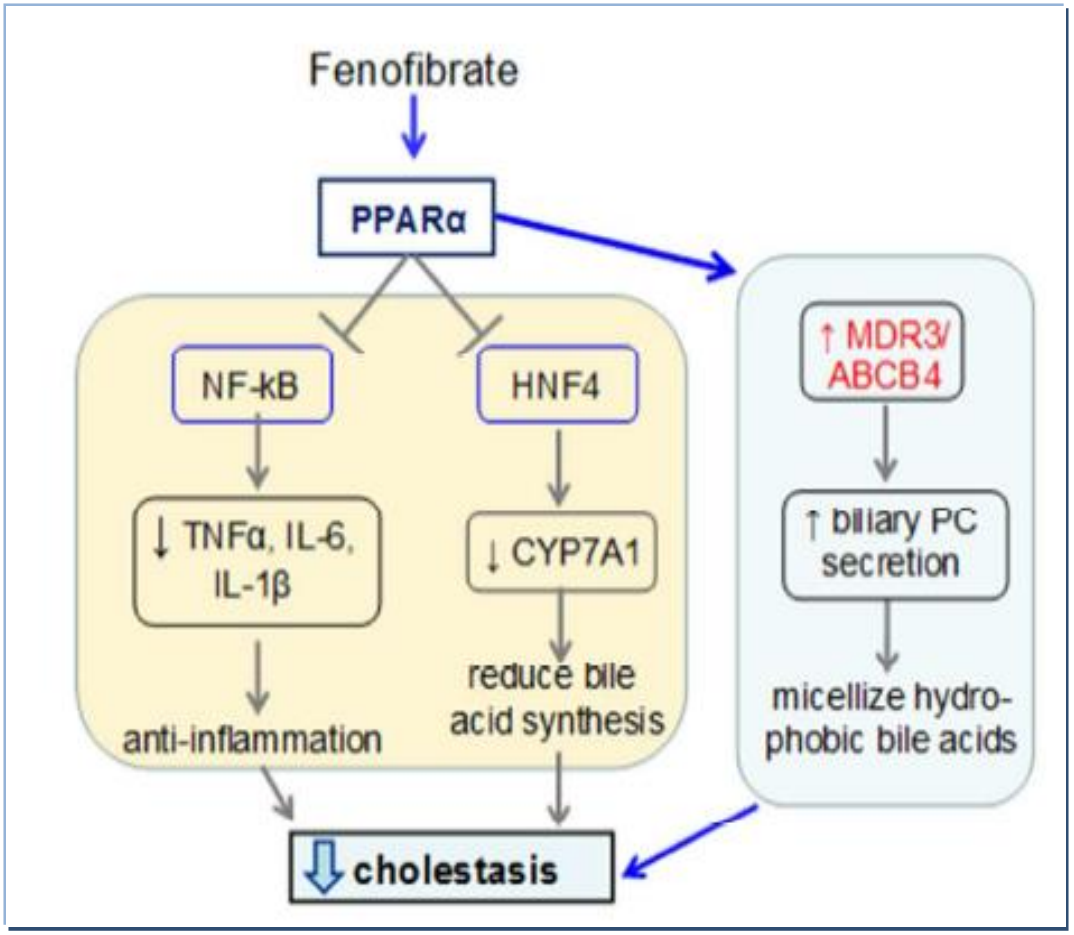
Mécanismes d'Action des Fibrates



+ action anti-inflammatoire

(Honda et al, Hepatology 2013)

Fibrates et Maladies Cholestatiques



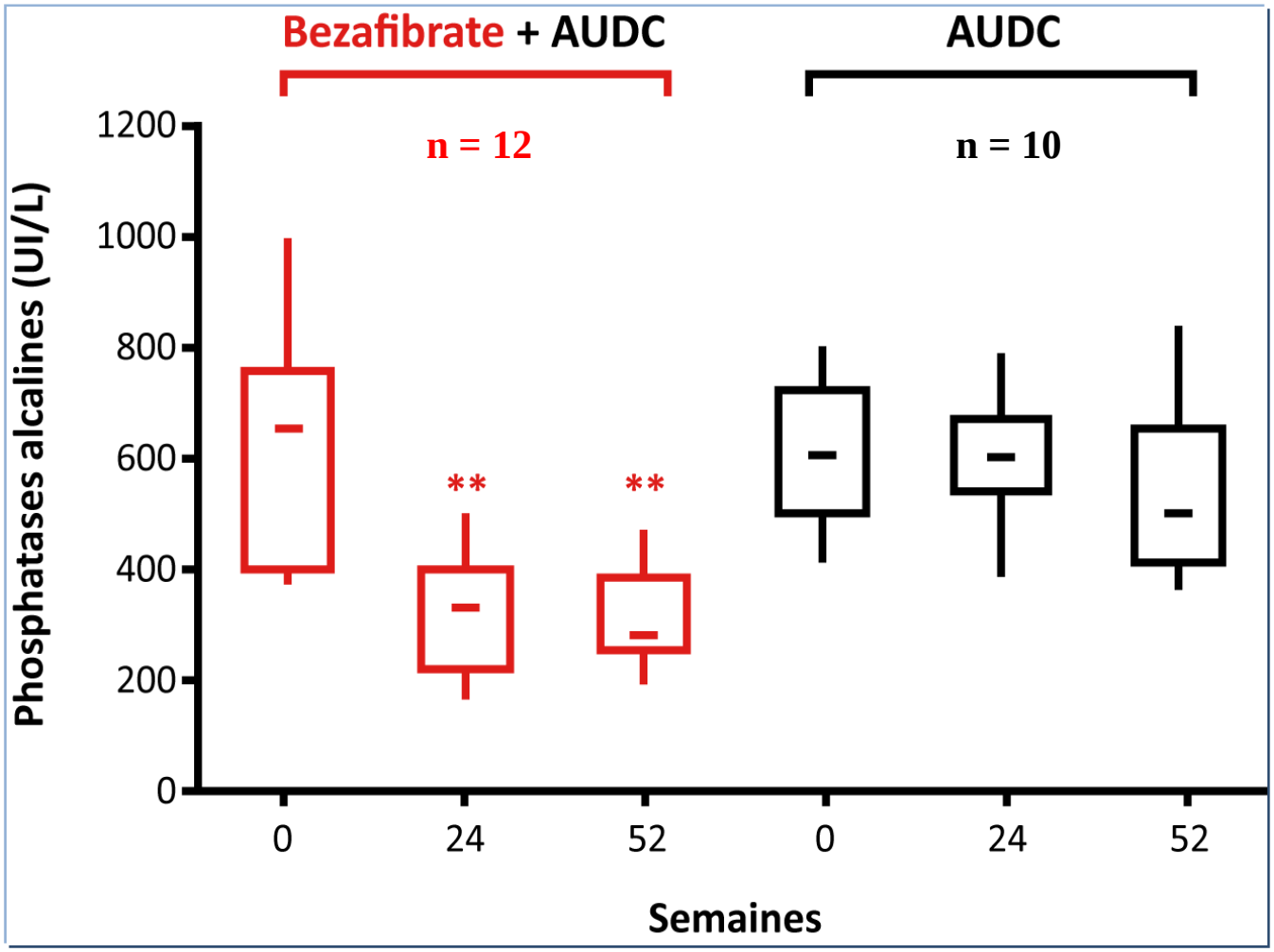
(Ghonem et al, Hepatology, 2015)

Table 2. Clinical studies testing fibrate treatment in PBC patients

Author	Year	Duration (months)	Fibrate (daily dose)	Patient number (treatment)	Tested in UDCA non-responders?	Outcome
Lens *et al.* [73▪]	2014	12	Bezafibrate (400 mg)	30 (UDCA + bezafibrate)	Yes[a]	↓ or ALP normalization, ↓ALT, ↓GGT, ↓cholesterol, ↓TG, ↓pruritus, liver stiffness unchanged
Honda *et al.* [68▪▪]	2013	3	Bezafibrate (400 mg)	19 (UDCA + bezafibrate)	Yes[b]	↓ALP, ↓ALT, ↓GGT, ↓IgM, ↓cholesterol, ↓TG, ↓C4, ↓FGF19
Han *et al.* [74]	2012	3–6	Fenofibrate (200 mg)	22 (UDCA + fenofibrate)	Yes[a]	↓ or ALP normalization, ↓AST, ↓ALT, ↓GGT, ↓cholesterol, ↓TG
Takeuchi *et al.* [75]	2011	12	Bezafibrate (400 mg)	15 (UDCA + bezafibrate)	Yes[a]	↓ or ALP normalization, ↓IgM, ↓cholesterol, ↓TG
Levy *et al.* [76]	2011	12	Fenofibrate (160 mg)	20 (UDCA + fenofibrate)	Yes[c]	↓ALP, ↓AST, ↓IgM, ↓IL1,6, ↑ApoAII, ↑ApoCII
Hazzan and Tur-Kaspa [77]	2010	4–12	Bezafibrate (400 mg)	8 (UDCA + bezafibrate)	Yes[b]	↓ or ALP normalization, ↓GGT
Liberopoulos *et al.* [78]	2010	2	Fenofibrate (200 mg)	6 (UDCA + fenofibrate), 4 (UDCA), randomized	Yes[d]	↓ALP, ↓ALT, ↓GGT, ↓cholesterol, ↓TG, ↓HDL
Walker *et al.* [79]	2009	23	Fenofibrate (134–200 mg)	16 (UDCA + fenofibrate)	Yes[a]	↓ or ALP normalization,↓IgM
Iwasaki *et al.* [80]	2008	12	Bezafibrate (400 mg)	20 (Bezafibrate), 25 (UDCA), randomized	Naive	↓ALP, ↓ALT, ↓GGT, ↓IgM, no difference between bezafibrate or UDCA monotherapy
Iwasaki *et al.* [80]	2008	12	Bezafibrate (400 mg)	12 (UDCA + bezafibrate), 10 (UDCA), randomized	Yes[e]	↓ or ALP normalization, ↓GGT, ↓IgM
Iwasaki *et al.* [96]	2007	not stated	Bezafibrate (400 mg)	28 (UDCA + bezafibrate)	Yes[b]	↓ or liver enzymes normalization (68%), progressive course of disease (32%), liver biopsy: improvement in 2 out of 3 cases
Kita *et al.* [81]	2006	6	Bezafibrate (400 mg)	22 (UDCA + bezafibrate or bezafibrate monotherapy)	5 Naive, 17 not stated	↓ALP, ↓GGT, ↓IgM
Ohmoto *et al.* [82]	2006	24–88	Bezafibrate (400 mg)	17 (UDCA + bezafibrate)	6 Naive, 11 not stated	↓serum markers of fibrosis (7s collagen, IV collagen, HA), ↓APRI score
Nakamuta *et al.* [83]	2005	25–53	Bezafibrate (400 mg) or fenofibrate (150 mg)	5 (UDCA + bezafibrate or fenofibrate)	Not stated	↓ALP, ↓ALT, ↓GGT, ↓IgM, ↓AMA
Akbar et al. [84]	2005	12	Bezafibrate (400 mg)	16 (10 UDCA + bezafibrate, 6 bezafibrate monotherapy)	10 Yes[b], 6 naive	↓ALP, ↓GGT, ↓cholesterol, ↓IgM, ↓nitrite production in isolated dendritic cells (as a measure for autoimmune disease progression)
Itakura *et al.* [85]	2004	12	Bezafibrate (400 mg)	9 (UDCA + bezafibrate), 7 (UDCA), randomized cross–over	Not stated	↓ALP, ↓GGT, ↓IgM, ↓TG
Dohmen *et al.* [86]	2004	3	Fenofibrate (100 or 150 mg)	9 (UDCA + fenofibrate)	Yes[f]	↓ALP, ↓IgM, and partially ↓ in AMA titer
Kanda *et al.* [87]	2003	6	Bezafibrate (400 mg)	11 (UDCA + bezafibrate), 11 (UDCA), randomized	Yes[b]	↓ALP, ↓GGT, bile acids unchanged
Ohira *et al.* [88]	2002	6	Fenofibrate (150–200 mg)	7 (UDCA + fenofibrate)	Yes[b]	↓ALP, ↓GGT, ↓IgM
Yano *et al.* [89]	2002	72–78	Bezafibrate (400 mg)	1 (UDCA + bezafibrate), 1 (bezafibrate)	1 Naive, 1 yes[f]	Normalization of ALP, progression of disease in liver histology in case 1 and stabilization in case 2
Kurihara *et al.* [90]	2002	36–60	Bezafibrate (400 mg)	3 (Bezafibrate)	Not stated	Case 1 and 2: ↓portal inflammation, case 3: no deterioration in liver histology (yearly biopsies during 3–5 years of bezafibrate treatment)
Ohmoto *et al.* [91]	2001	12	Bezafibrate (400 mg)	10 (UDCA + bezafibrate)	Yes[f]	↓ or normalization of ALP, GGT, ALT, and IgM, ↓fatigue and pruritus
Kurihara *et al.* [92]	2000	12	Bezafibrate (400 mg)	12 (Bezafibrate), 12 (UDCA), randomized	Naive	↓ALP, ↓GGT, ↓IgM, bezafibrate monotherapy more effective than UDCA
Nakai *et al.* [93]	2000	12	Bezafibrate (400 mg)	10 (UDCA + bezafibrate), 13 (UDCA), randomized	Not stated	↓ALP, ↓GGT, ↓IgM
Miyaguchi *et al.* [94]	2000	6	Bezafibrate (not stated)	13 (UDCA + bezafibrate)	Yes[b]	↓ALP, ↓ALT, ↓GGT, ↓IgM, ↓IgG
Iwasaki *et al.* [95]	1999	12–21	Bezafibrate (400 mg)	11 (7 UDCA + bezafibrate, 4 bezafibrate)	9 Yes[f], 2 naive	↓ALP, ↓ALT, ↓GGT, ↓IgM ↓fatigue and pruritus

(Cuperus et al, 2014)

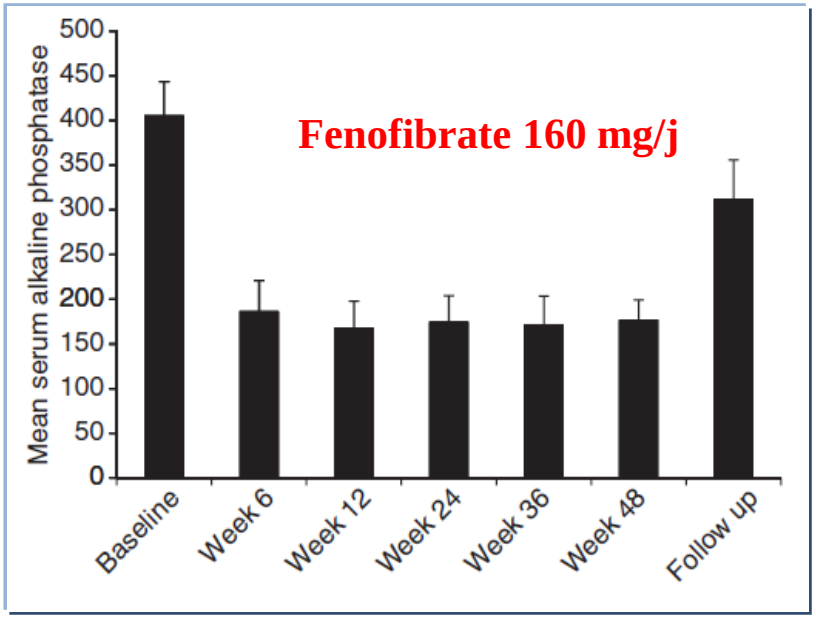
Fibrates et CBP (1)



(Iwasuki et al, Hepatol research 2008)

Fibrates et CBP (2)

- **20 CBP avec PAL ≥ 2 N sous AUDC**



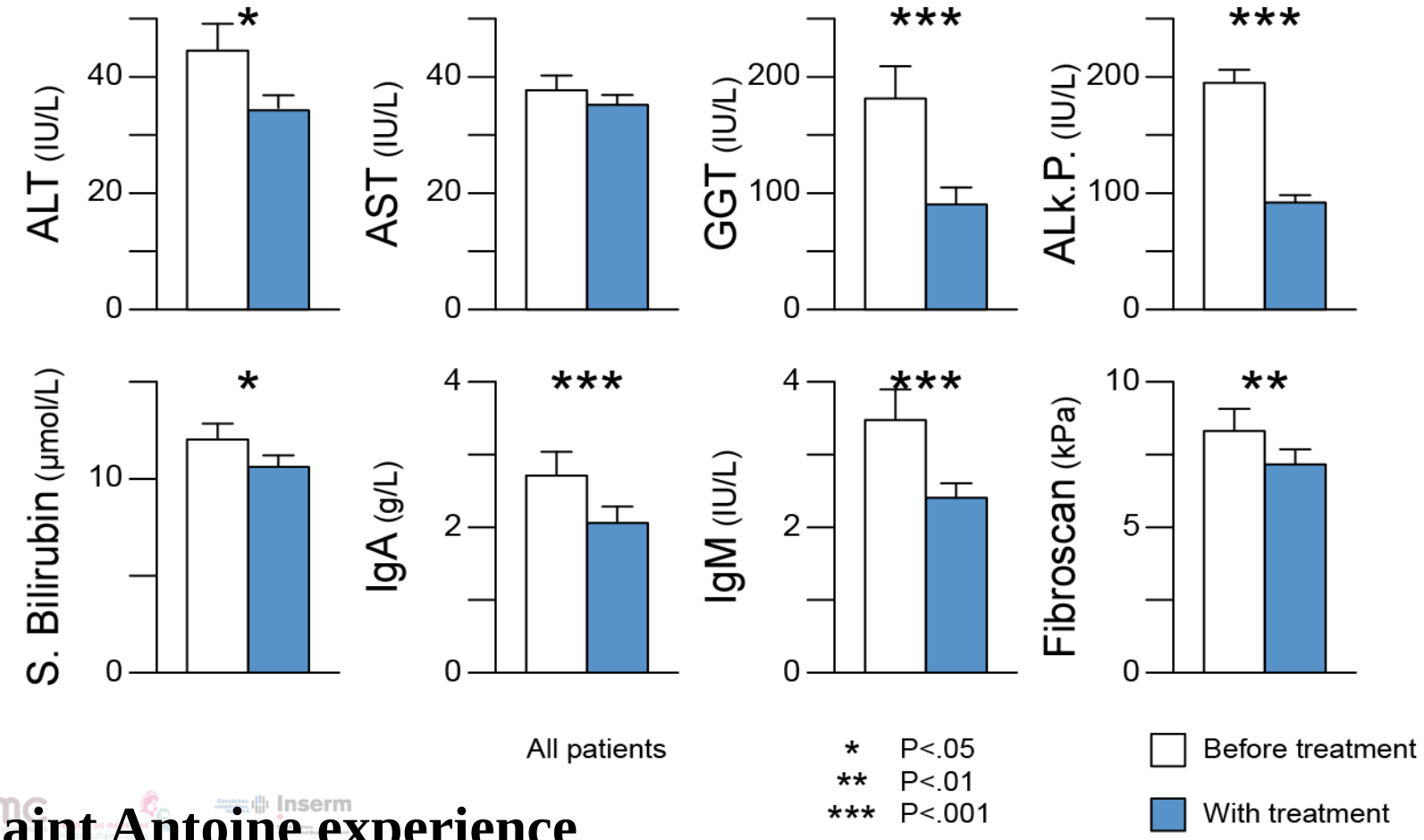
n	Adverse event	Severity/duration	Relationship to study drug
5	Heartburn	Severe in 2 patients	Probably related
2	Elevated ALT and AST	Moderate (2-5x), transient	Probably related
3	Nausea	Mild, transient	Possibly related
1	Arthralgias	Mild, persistent	Possibly related
1	Weight gain	Mild	Possibly related

Myalgies ? Pas de dosage systématique CPK

(Levy et al, Aliment Pharmacol Ther 2011)

- **Amélioration franche du prurit sous Bezafibrate (400 mg/j):**
  27 CBP avec prurit sous AUDC ***(Pares et al, AASLD 2015)***
  - **Disparition: 17, amélioration partielle: 7**
  - **A l'arrêt du bezafibrate: récidive constante**

Fenofibrate (200 mg/j) chez les Patients Ne Répondant pas à l'AUDC Seul (3)

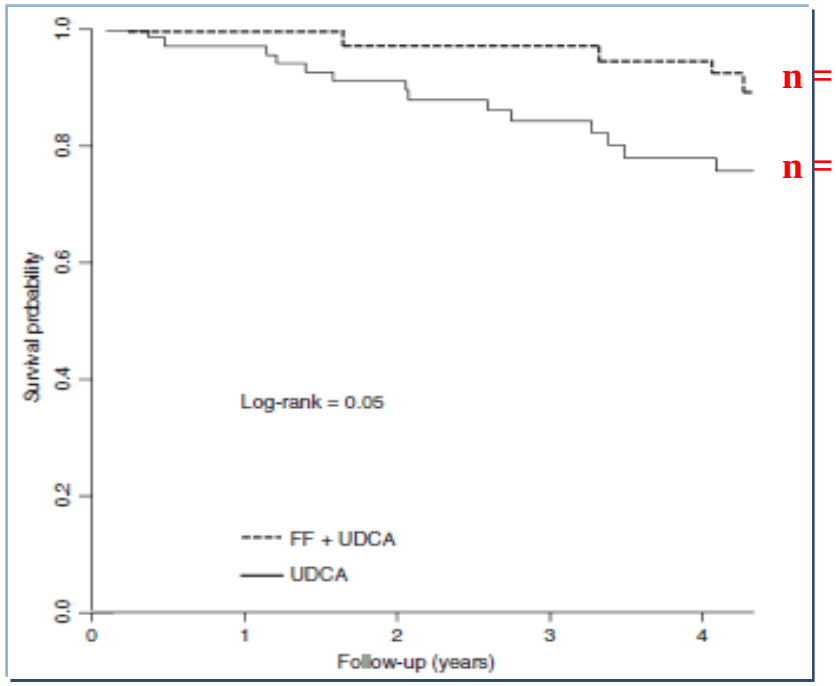


Saint Antoine experience

29 CBP, suivi: 2 ans

Fibrates et CBP (4)

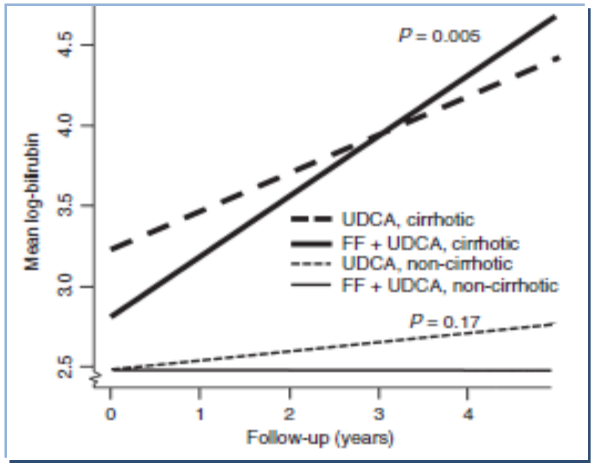
- **Etude rétrospective: Feno 145 mg/j**



(Cheung et al, Aliment Pharmacol Ther 2016)

Table 4 | Adverse events in patients receiving combined fenofibrate and UDCA therapy and UDCA monotherapy

Adverse event	FF + UDCA, *n* = 46	UDCA, *n* = 74	*P*-value
Subjective			
Abdominal pain	2 (17)	0	0.15
Myalgia*	2 (17)	0	0.15
Headache*	1 (8)	0	0.38
Angioedema	1 (8)	0	0.38
Pedal oedema	1 (8)	0	0.38
Pruritus	1 (8)	0	0.38
Objective			
Hepatitis (>5× ULN)	1 (8)†	0	0.38
Creatinine rise (doubling)	1 (8)†	0	0.38
Bilirubin rise (doubling)	2 (17)	0	0.15

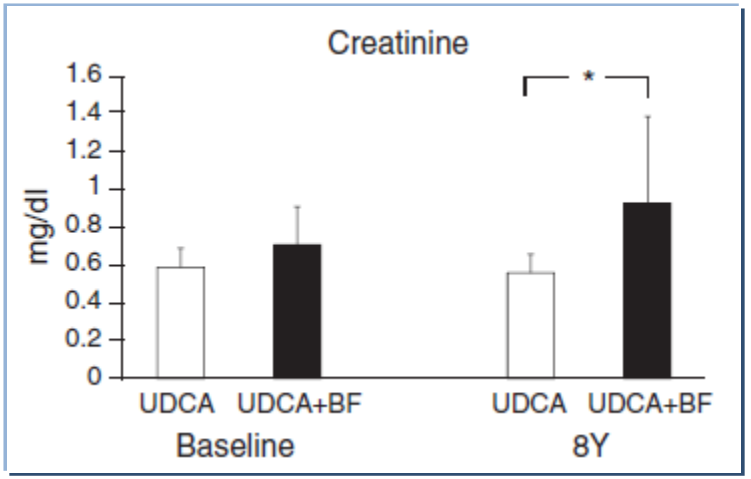


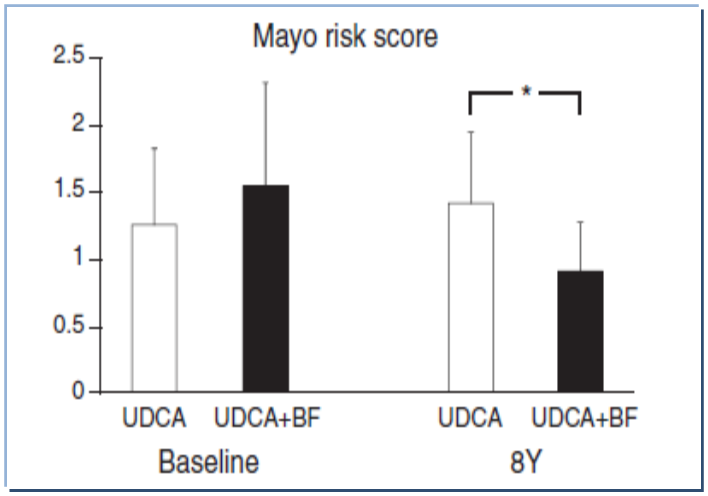
A Prospective Randomized Controlled Study of Long-Term Combination Therapy Using Ursodeoxycholic Acid and Bezafibrate in Patients With Primary Biliary Cirrhosis and Dyslipidemia

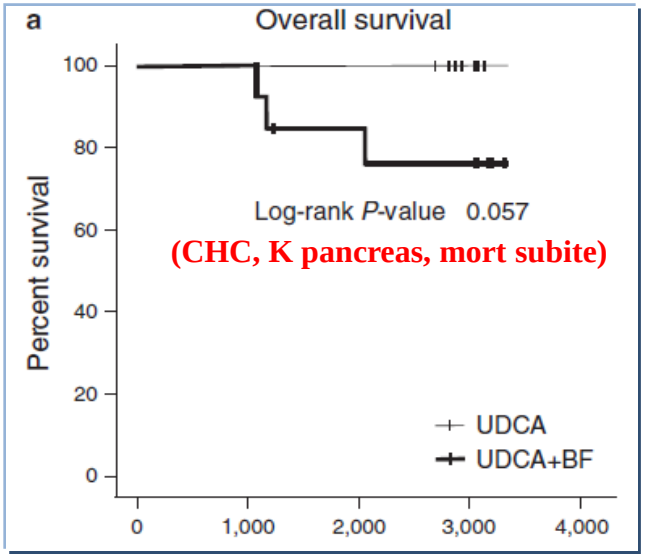
(Hosonuma et al, Am J Gastroenterol 2015)

Table 2. Adverse events and dose reduction/discontinuation

	UDCA (*n*=14)	UDCA+BF (*n*=13)	*P*
Subjective and objective symptoms	0	2	0.222
Muscle pain (*n*)	0	1	0.481
Leg edema (*n*)	0	1	0.481
Abnormal laboratory findings (n)	0	3	0.098
Renal dysfunction (*n*)	0	2	0.222
Elevation of CPK (*n*)	0	1	0.481
Dose reduction/discontinuation (n)	0	3	0.098
[a]Dose reduction (*n*)	0	1	0.481
[b]Discontinuation (*n*)	0	2	0.222







Essai de phase 3 BEZURSO

EDITORIALS

No more pilots, a phase III trial of fibrates in primary biliary cirrhosis is long overdue!

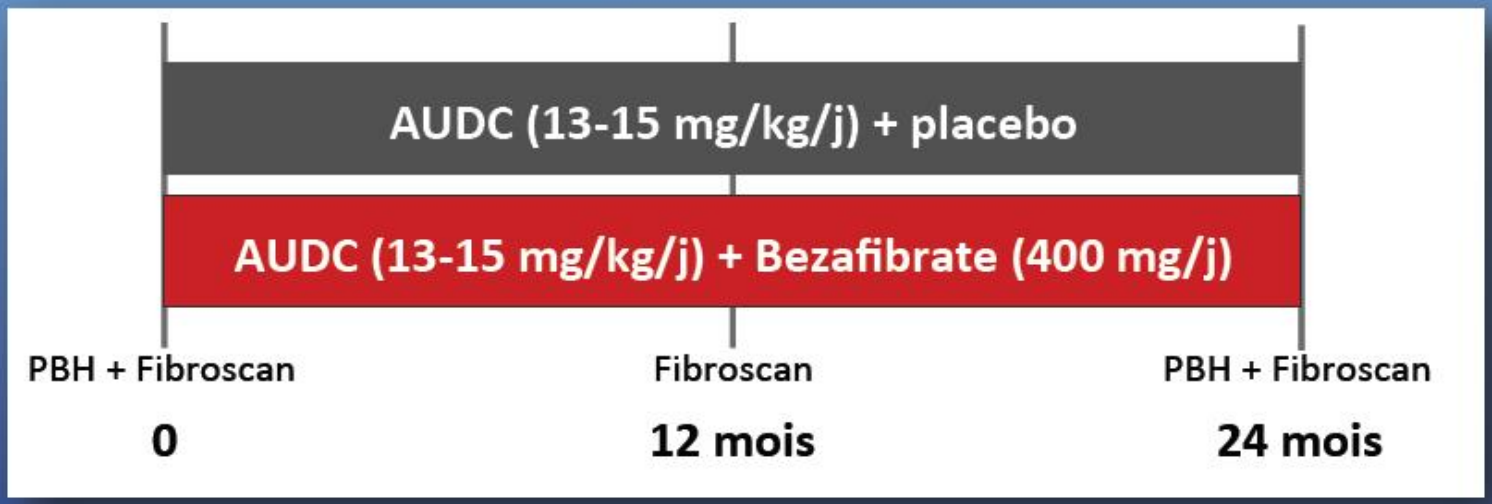
John S Halliday and Roger W Chapman

Department of Hepatology, John Radcliffe Hospital, Headington, Oxford, UK

See article in *J. Gastroenterol. Hepatol.* 2011; 26: 1395–1401.

Critères de sélection:

Patients avec réponse biochimique incomplète définie par des PAL > 1,5N après 6 mois d'AUDC.



100 patients (1/1) répondeurs incomplets (Paris 2) inclus au 31/12/14

Critère principal: normalisation des tests hépatiques

Résultats attendus: mi-2017…. **MERCI +++**

PBC Management
(en l'absence d'essai thérapeutique)