Traitement de 2ème intention de la CBP: les Fibrates

Christophe CORPECHOT

Centre de référence des maladies inflammatoires des voies biliaires
et des hépatites auto-immunes (MIVB-H)

Hôpital Saint-Antoine, APHP

Inserm UMR S938, Sorbonne Université

10ème journée des CRMR et CCMR MIVB-H, vendredi 24 mai 2019, Paris

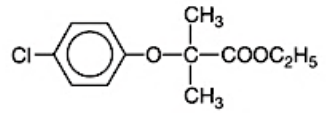
MIVB-H
CENTRE DE RÉFÉRENCE
MALADIES INFLAMMATOIRES
DES VOIES BILIAIRES ET
HÉPATITES AUTO-IMMUNES

Liens d’intérêt

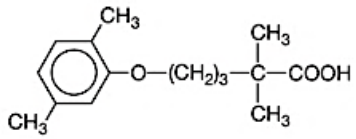
- **Arrow**
- **Intercept**
- **GSK**
- **Inventiva**
- **Cymabay**
- **Enanta**

Fibrates (dérivés de l'acide fibrique)

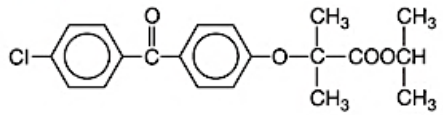
CLOFIBRATE



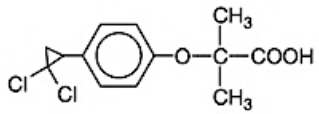
GEMFIBROZIL



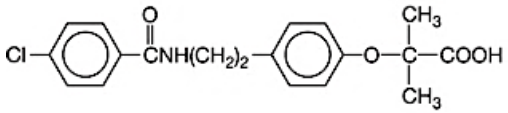
FENOFIBRATE



CIPROFIBRATE



BEZAFIBRATE



- Hypolipémiants découverts dans les années 60
- ↑ β-oxydation des acides gras
- ↓ VLDL, ↑ HDL
- ↓↓ Triglycérides, ↓ Cholestérol
- ↓ Inflammation
- **Agonistes PPAR-α**
- Affinité variable pour PPAR-δ et PPAR-γ

Peroxisome Proliferator-Activated Receptors (PPARs)

PPAR-α

- Métabolisme lipidique
- Forte expression dans le foie
- Agonistes: Acides gras, **Fibrates**

PPAR-δ

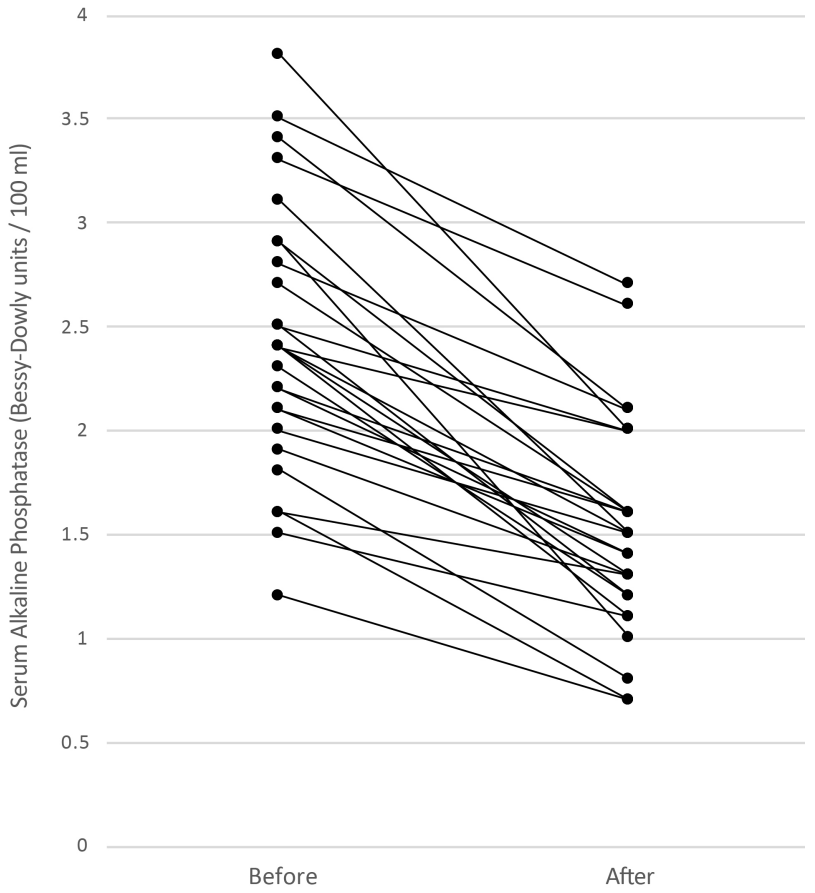
- Métabolisme glucido-lipidique
- Expression ubiquitaire
- Agonistes: Acides gras, Seladelpar, Bezafibrate, Elafibranor

PPAR-γ

- Métabolisme glucido-lipidique et énergétique
- Forte expression tissu adipeux
- Agonistes: Acides gras, Thiazolidinediones

Réduction des PAL sous Fibrates: 1ère description en 1963!

- Observation empirique
- 41 patients avec dyslipidémie
- Clofibrate: 1,5 à 2 g/ jour
- Durée médiane: 3 mois
- ↓ des PAL de 37% (p<.0001)
- Fraction hépatique des PAL



D'après Hellman et al. Ann Intern Med 1963

Fibrates et CBP: première observation en 1999

ELSEVIER

Hepatology Research 16 (1999) 12–18

Hepatology Research

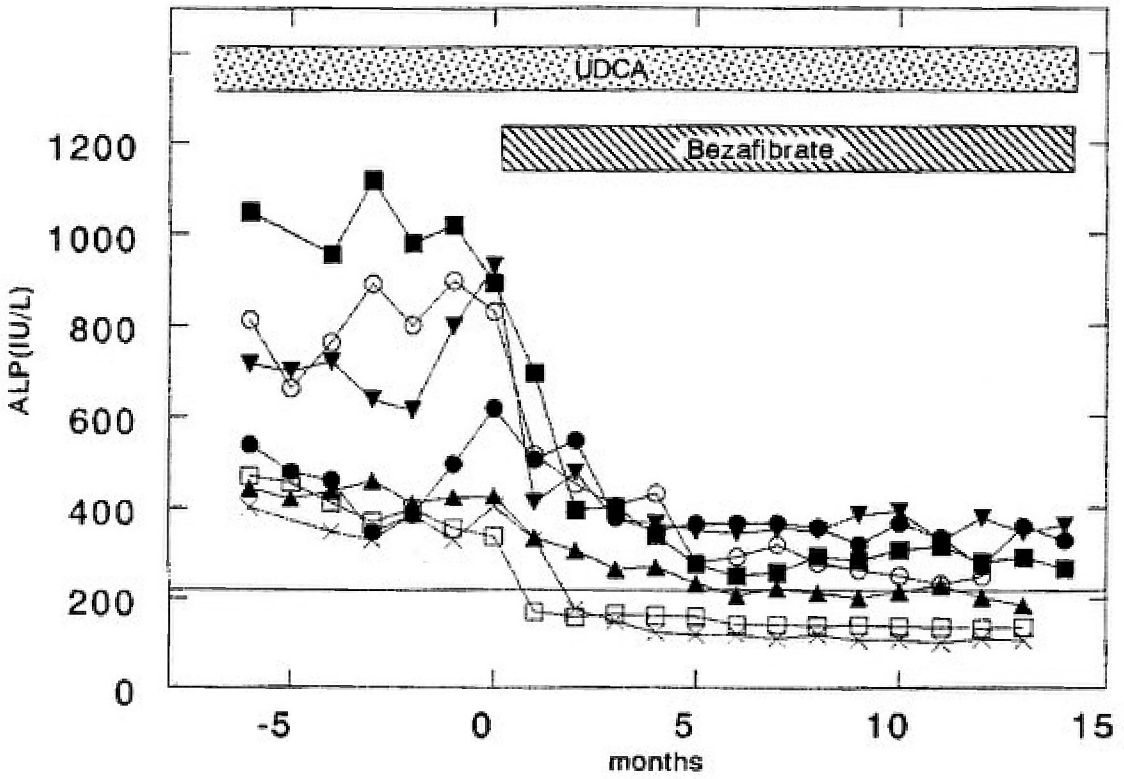
www.elsevier.com/locate/ihepcom

Bezafibrate may have a beneficial effect in pre-cirrhotic primary biliary cirrhosis

Shinji Iwasaki *, Keisuke Tsuda, Hiroshi Ueta, Rei Aono, Masafumi Ono, Toshiji Saibara, Takashi Maeda, Saburo Onishi

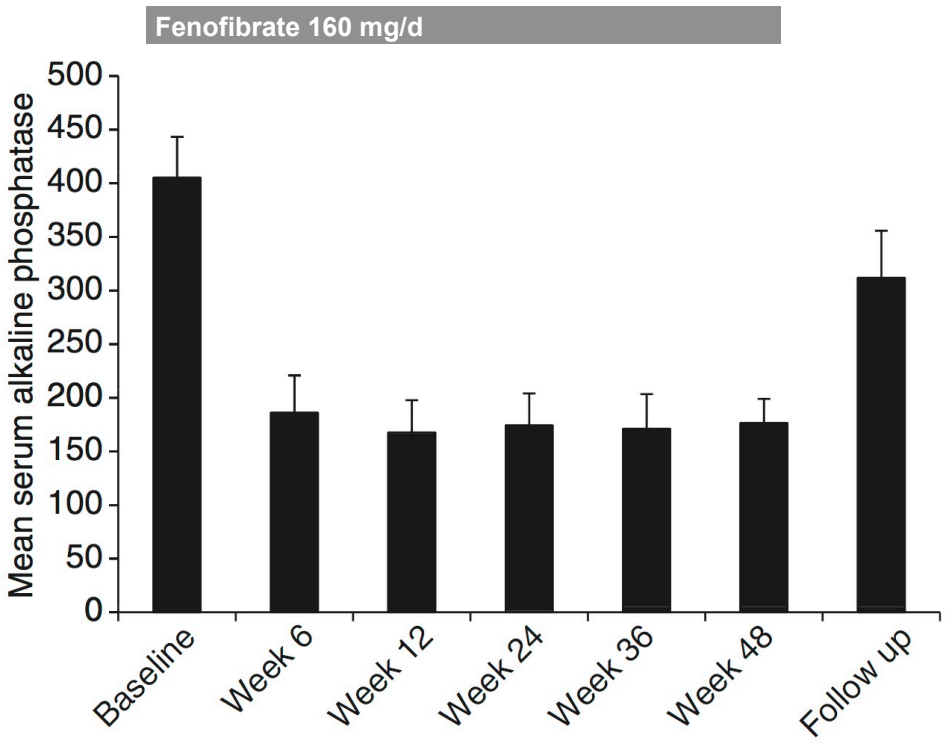
First Department of Internal Medicine, Kochi Medical School, Kohasu, Oko, Nankoku, Kochi, 783-8505 Japan

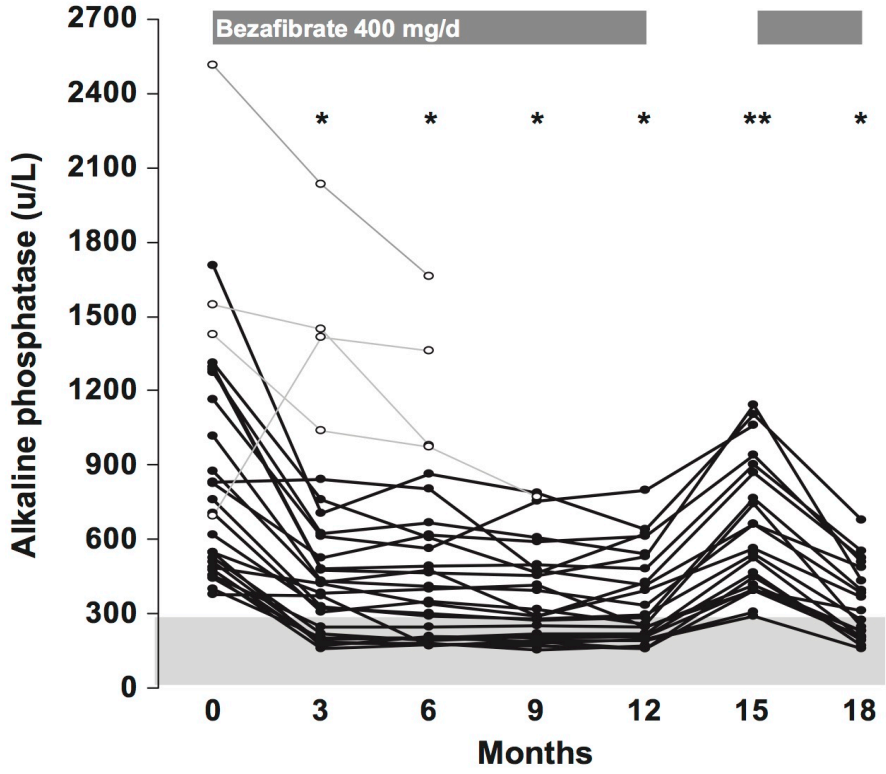
Received 13 January 1999; received in revised form 14 April 1999; accepted 28 April 1999



Iwasaki et al. Hepatol Res 1999

Fibrates et CBP: observations concordantes

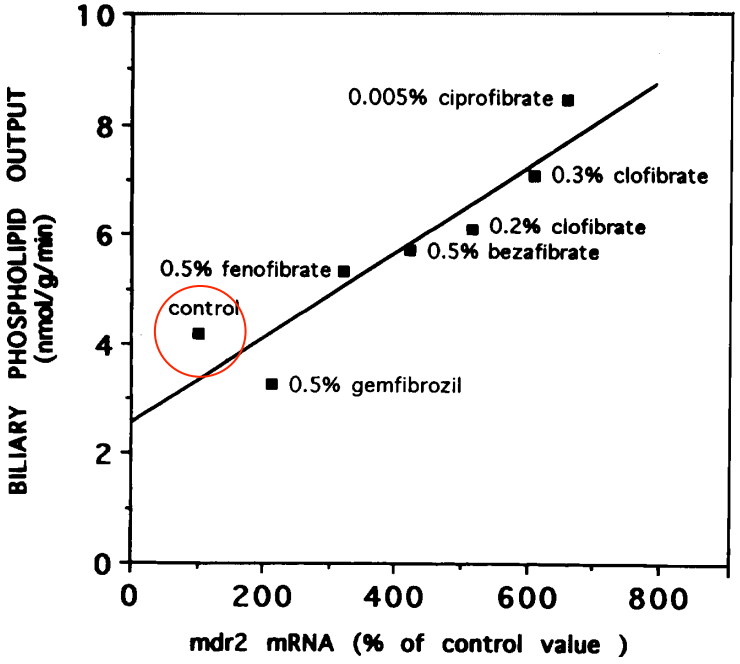




Levy et al. Aliment Pharmacol Ther 2011
Lens et al. Liver Int 2014

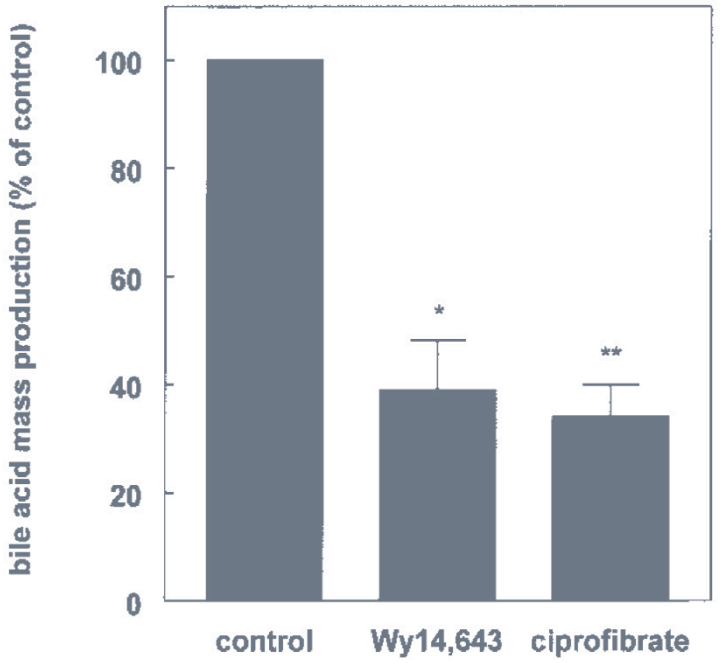
Fibrates et sécrétion biliaire

Induction de ABCB4 (MDR3)



Chianale et al. Biochem J 1996

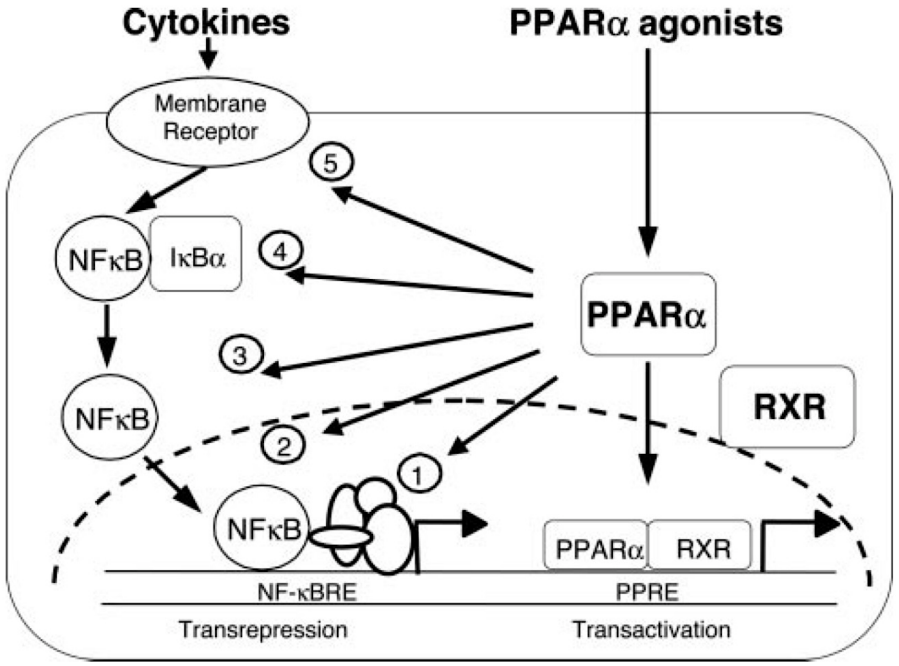
Inhibition de CYP7A1 et NTCP



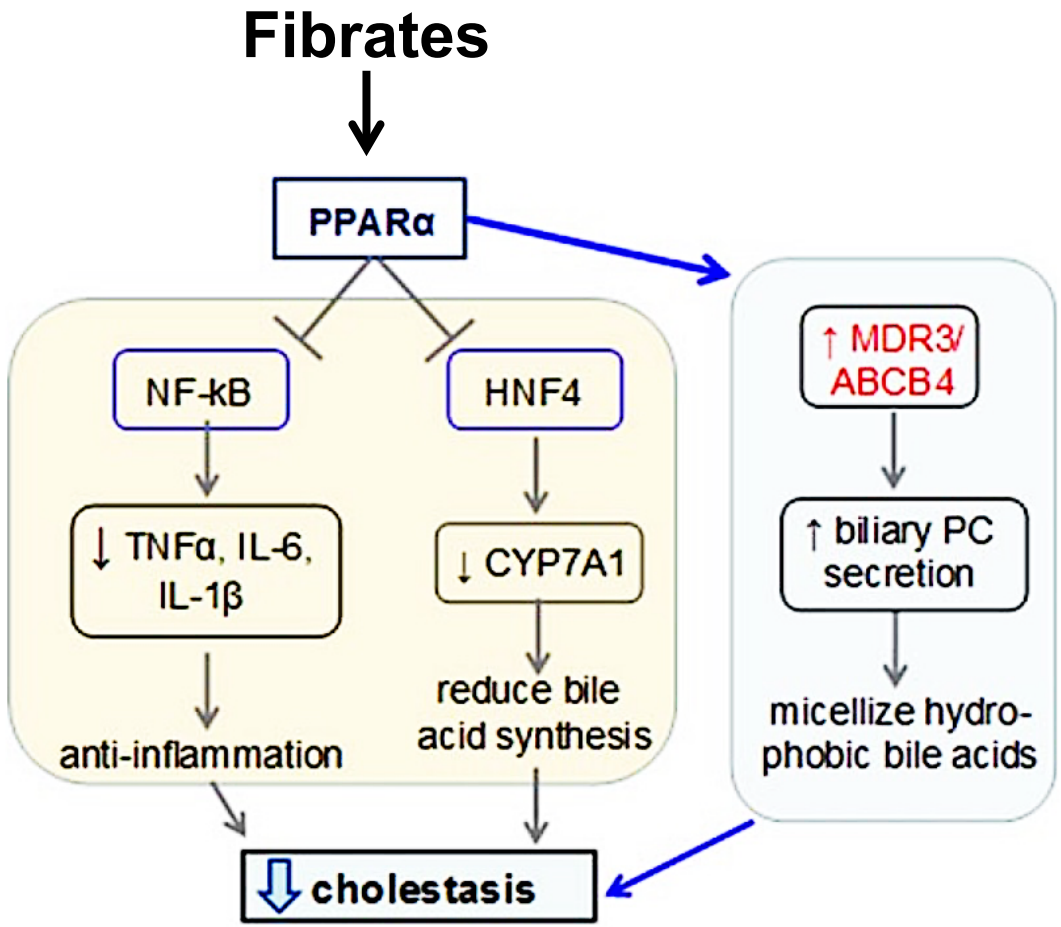
Post et al. Arterioscler Thromb Vasc Biol 2001

Fibrates et inflammation

↓ NFkB

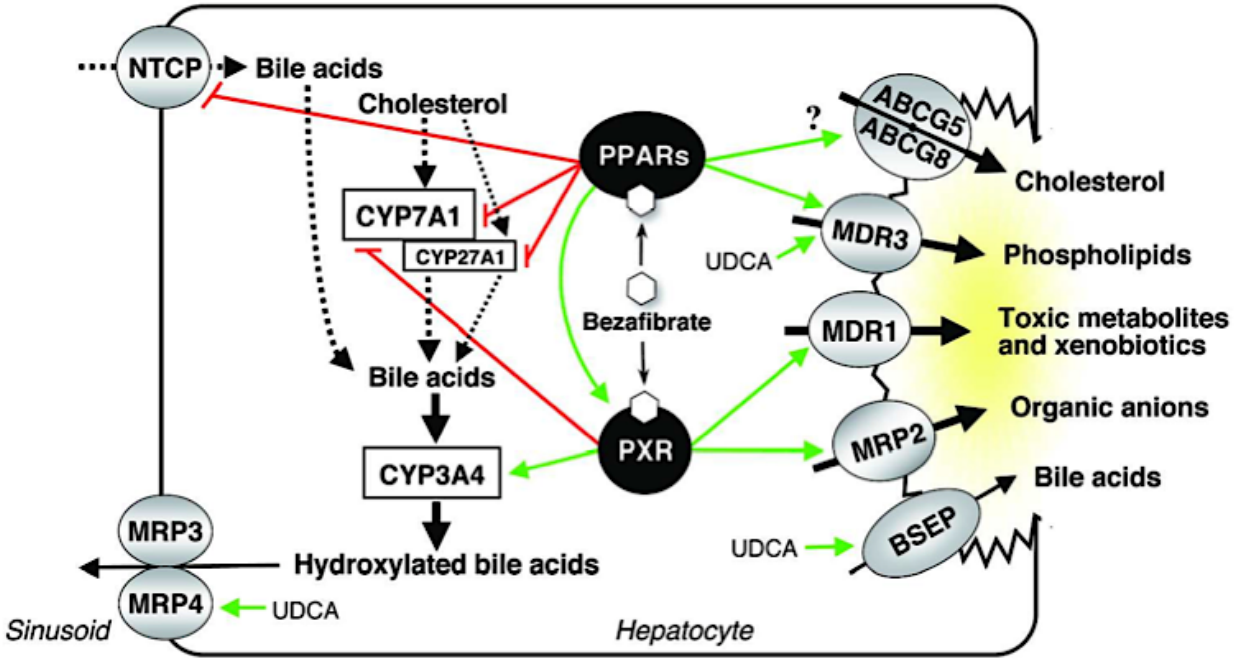


Inhibition de NFkB



Staels et al. Nature 1998
Ghonem et al. Hepatology 2015

Bezafibrate: double agoniste pan-PPAR et PXR

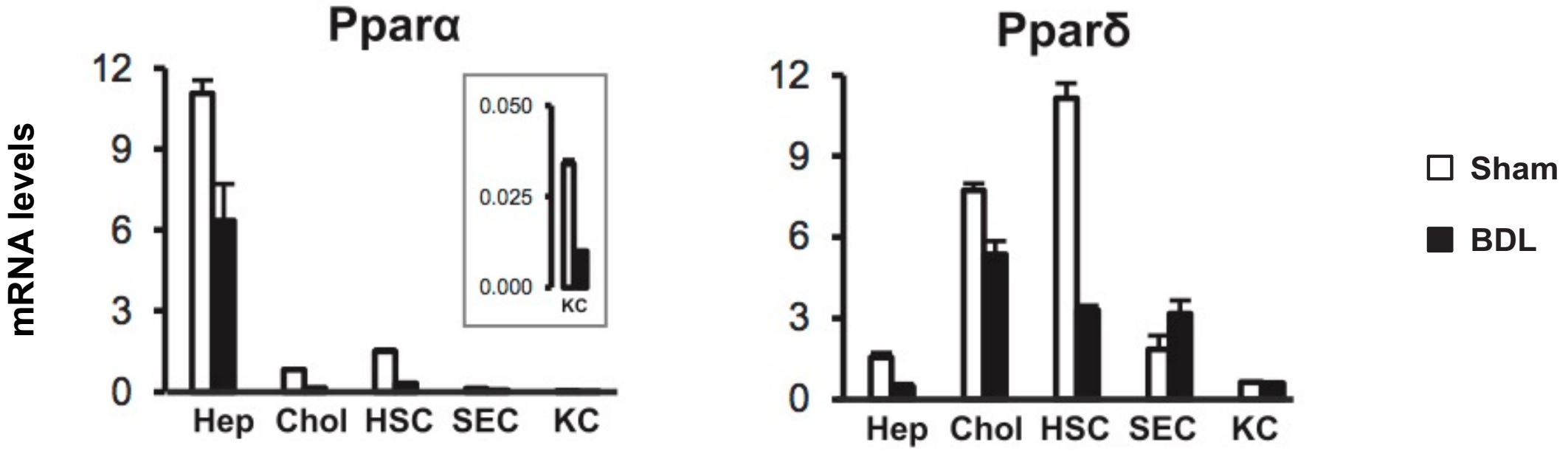


Honda et al. Hepatology 2013

Bezafibrate: agent multi-cibles

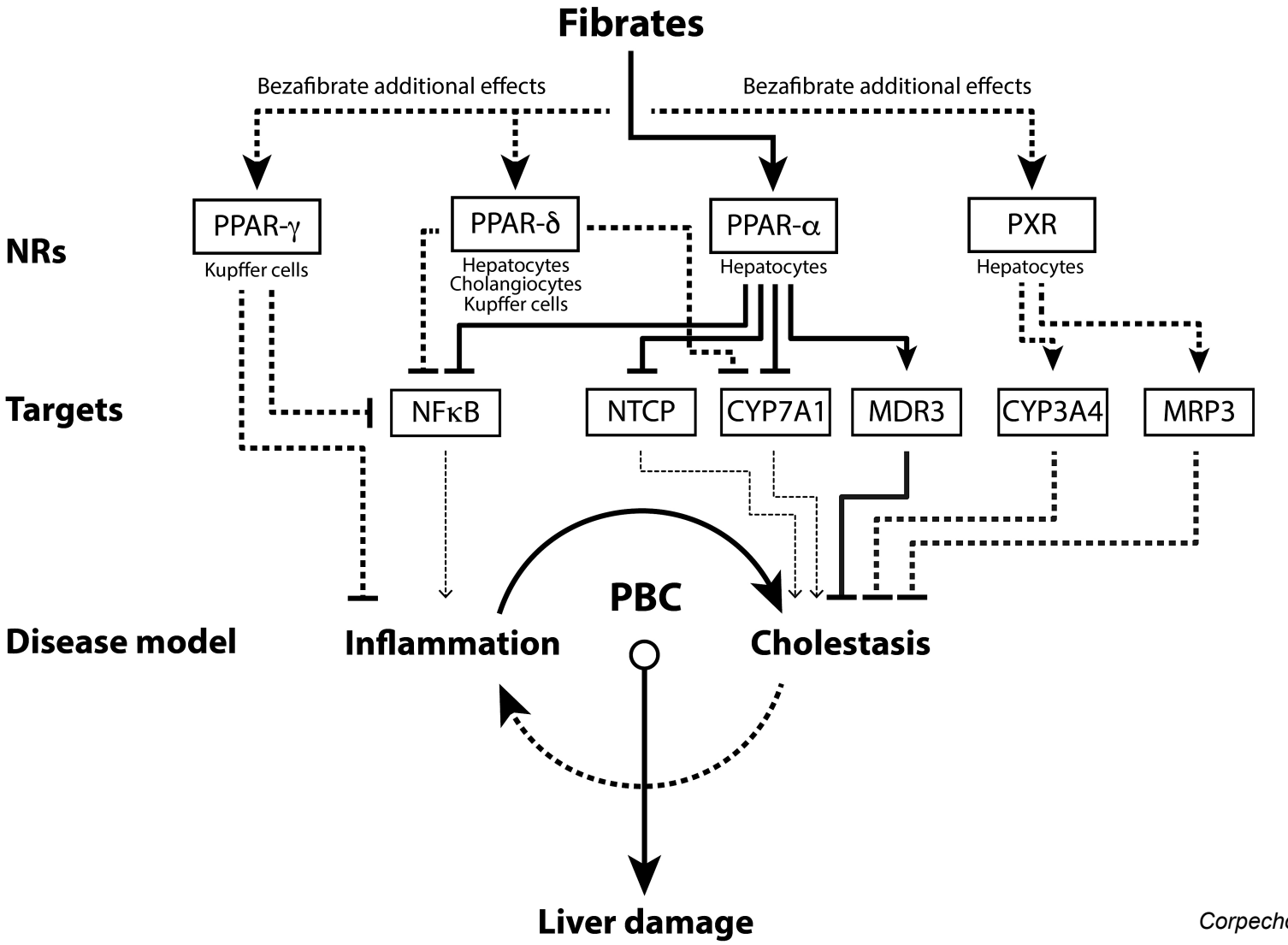
	Effet anti-cholestatique	Effet anti-inflammatoire
PPAR-α	✓	✓
PPAR-δ	✓	✓
PPAR-γ		✓
PXR	✓	✓

Expression hépatique de PPAR-α et PPAR-δ



Gonzalez-Sanchez et al. Biochim Biophys Acta 2017

Agonistes PPARs et CBP: mécanismes



Corpechot. Curr Hepatol Rep 2019

CBP et Fibrates: 18 ans d'attente pour une phase 3

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.

CBP et Bezafibrate: étude BEZURSO

The NEW ENGLAND JOURNAL of MEDICINE

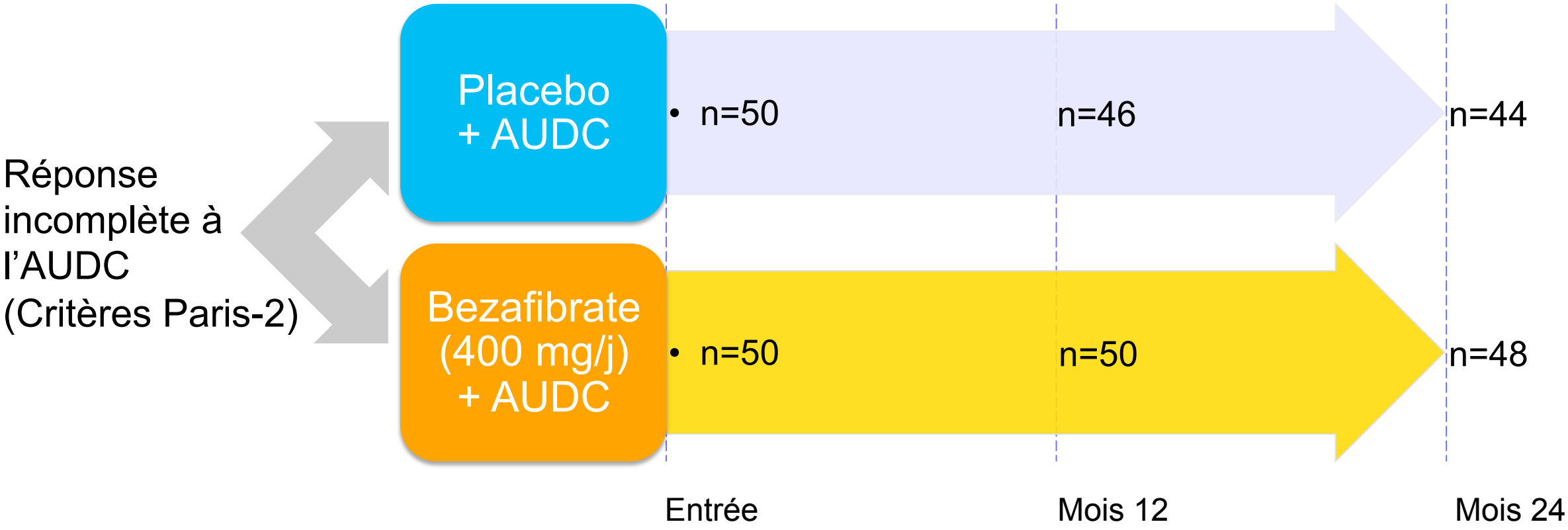
ORIGINAL ARTICLE

A Placebo-Controlled Trial of Bezafibrate in Primary Biliary Cholangitis

C. Corpechot, O. Chazouillères, A. Rousseau, A. Le Gruyer, F. Habersetzer, P. Mathurin, O. Goria, P. Potier, A. Minello, C. Silvain, A. Abergel, M. Debette-Gratien, D. Larrey, O. Roux, J.-P. Bronowicki, J. Boursier, V. de Ledinghen, A. Heurgue-Berlot, E. Nguyen-Khac, F. Zoulim, I. Ollivier-Hourmand, J.-P. Zarski, G. Nkontchou, S. Lemoinne, L. Humbert, D. Rainteau, G. Lefèvre, L. de Chaisemartin, S. Chollet-Martin, F. Gaouar, F.-H. Admane, T. Simon, and R. Poupon

Corpechot et al. N Engl J Med 2018

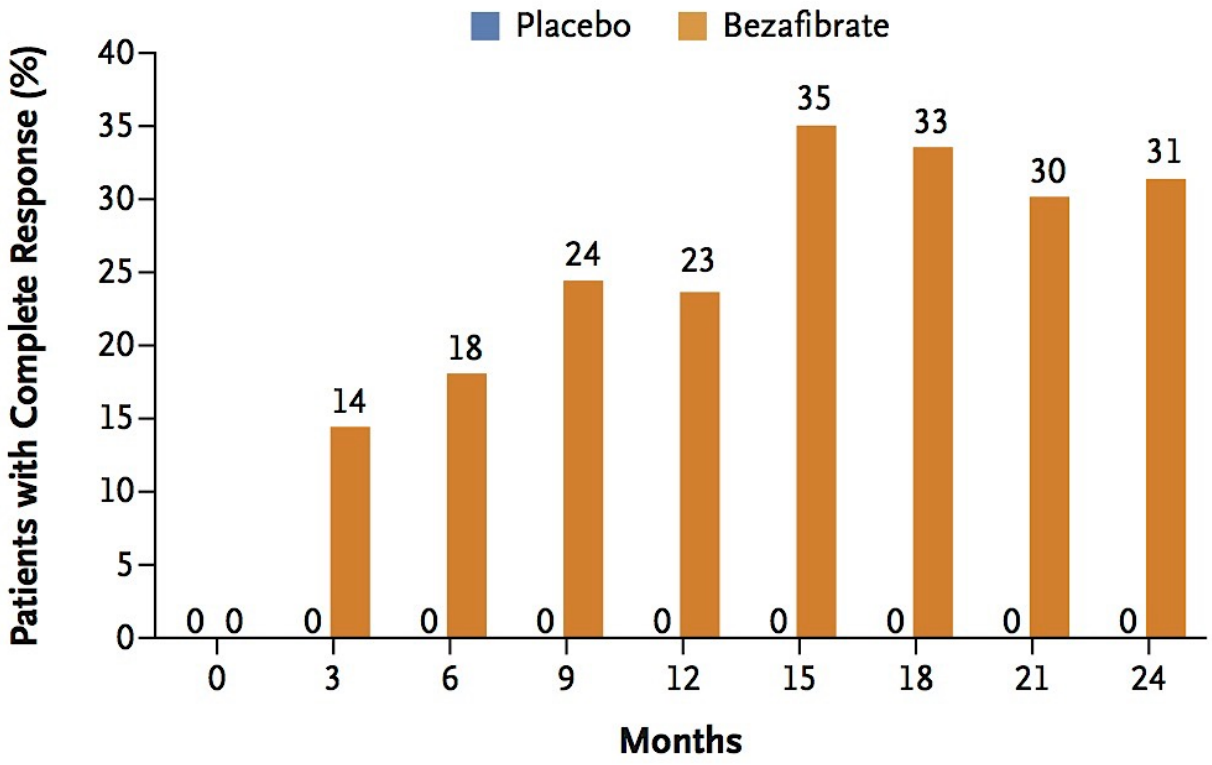
Etude BEZURSO: design



Etude BEZURSO: critère de jugement principal

Réponse biologique complète:

- **Bilirubine normale**
- **PAL normales**
- **Transaminases normales**
- **Albumine normale**
- **TP normal**

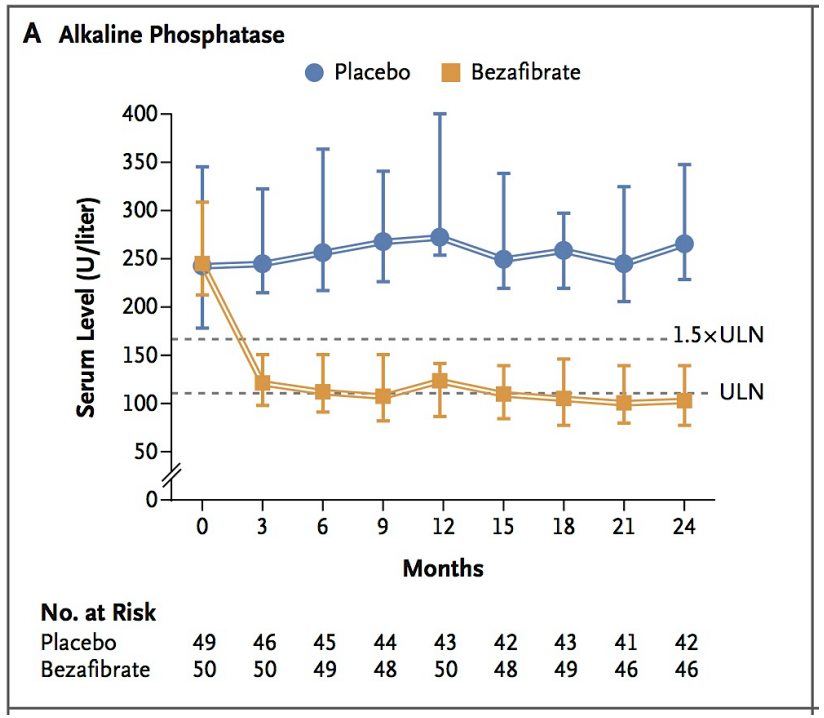


No. at Risk									
Placebo	46	41	41	39	41	36	36	36	39
Bezafibrate	47	49	45	41	47	43	45	40	45

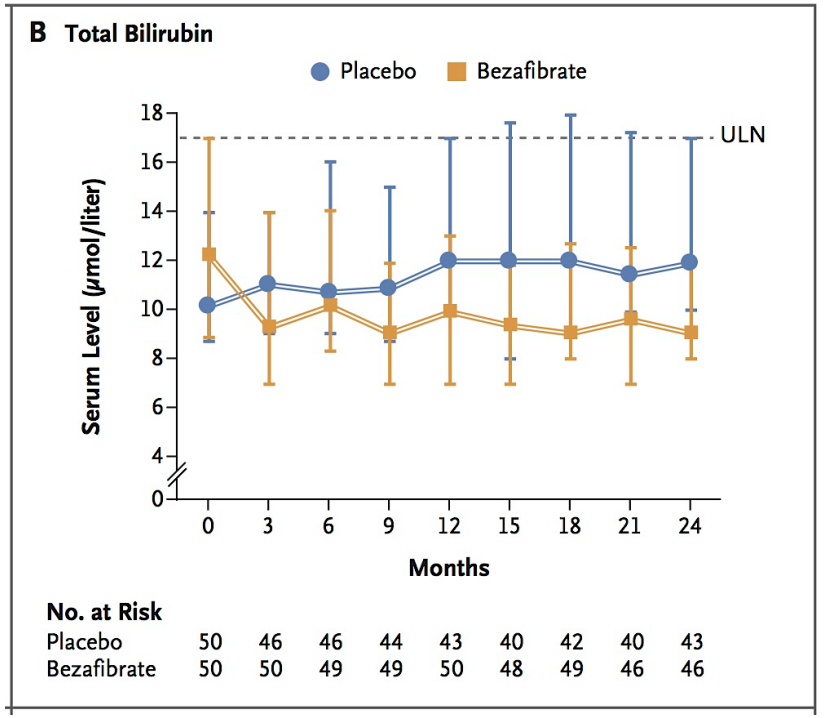
Corpechot et al. N Engl J Med 2018

Etude BEZURSO: principaux effets biochimiques

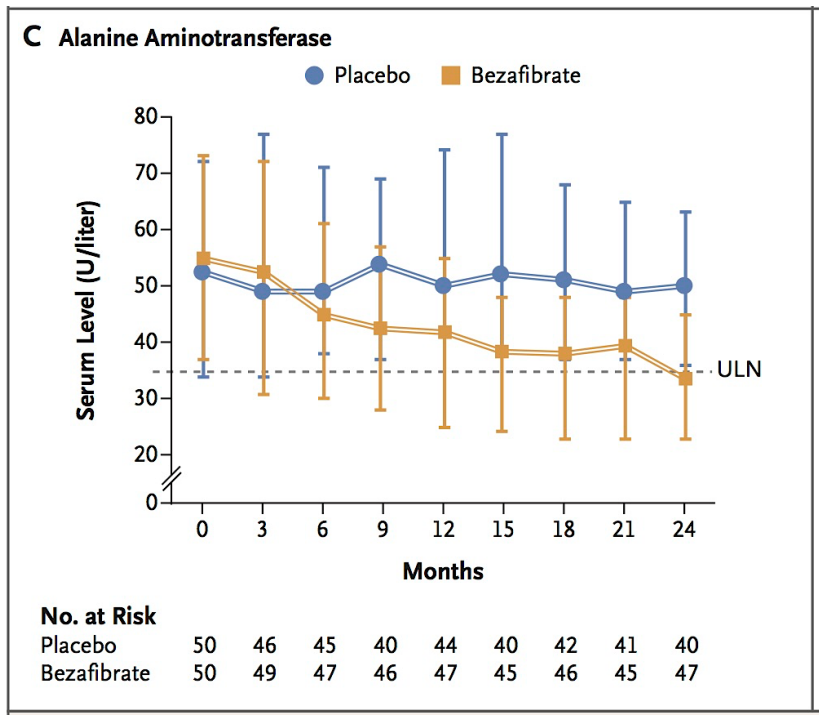
PAL



Bilirubine

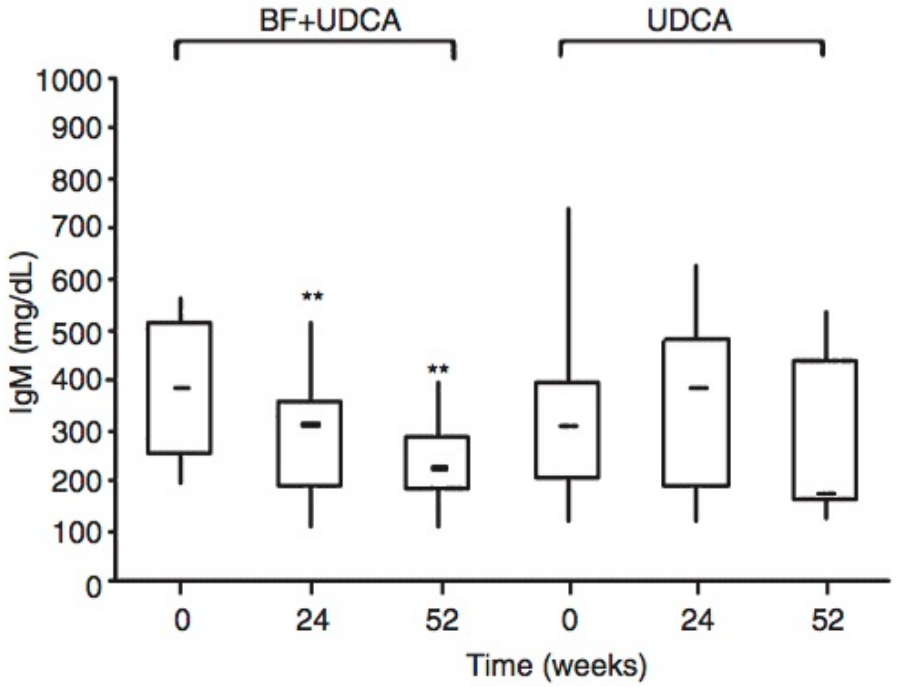


ALAT

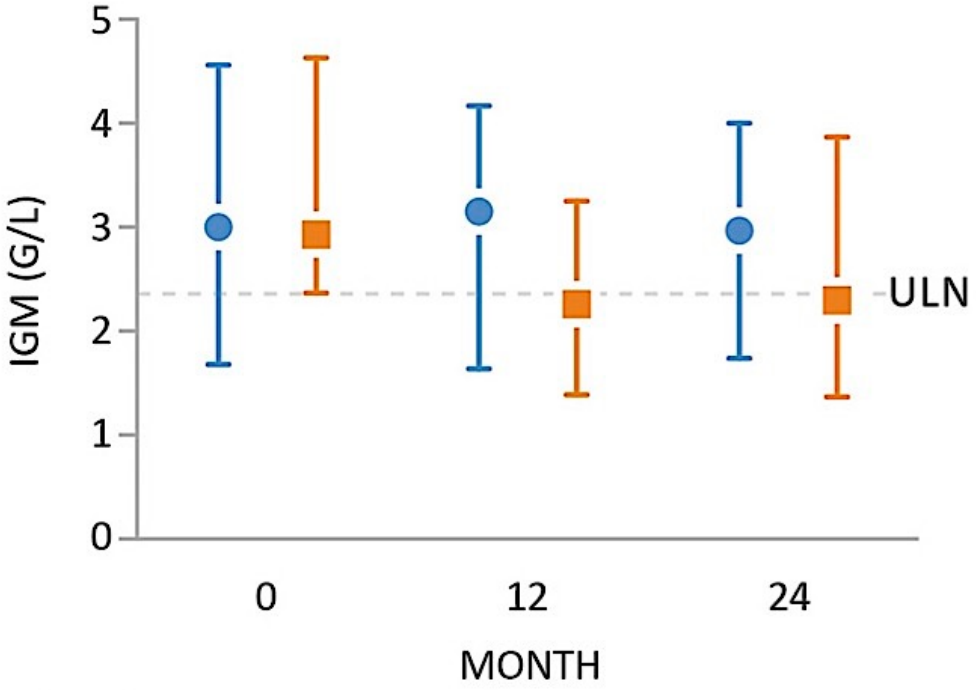


Corpechot et al. N Engl J Med 2018

CBP et Fibrates: effet sur les IgM

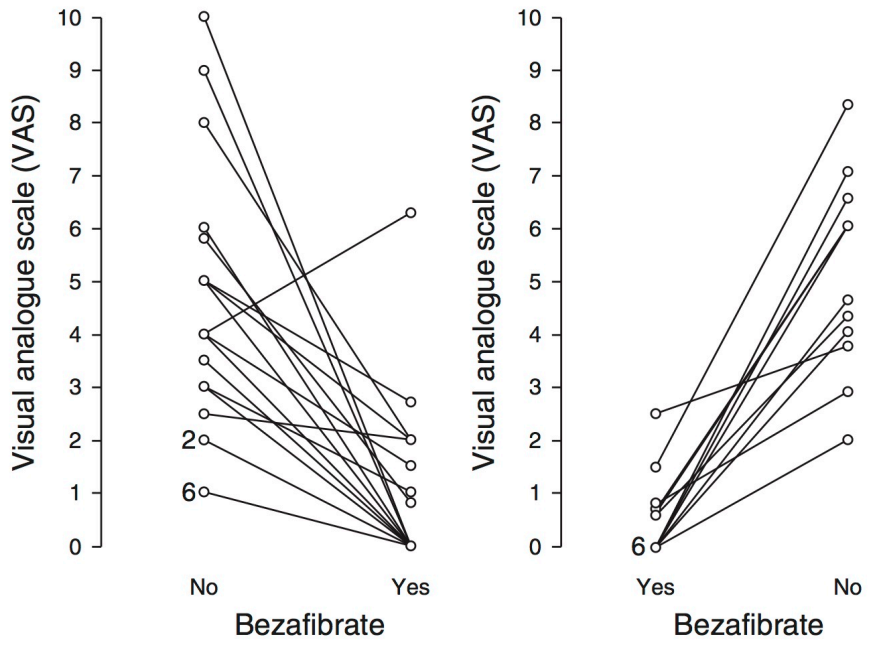


Iwasaki et al. Hepatol Res 2008

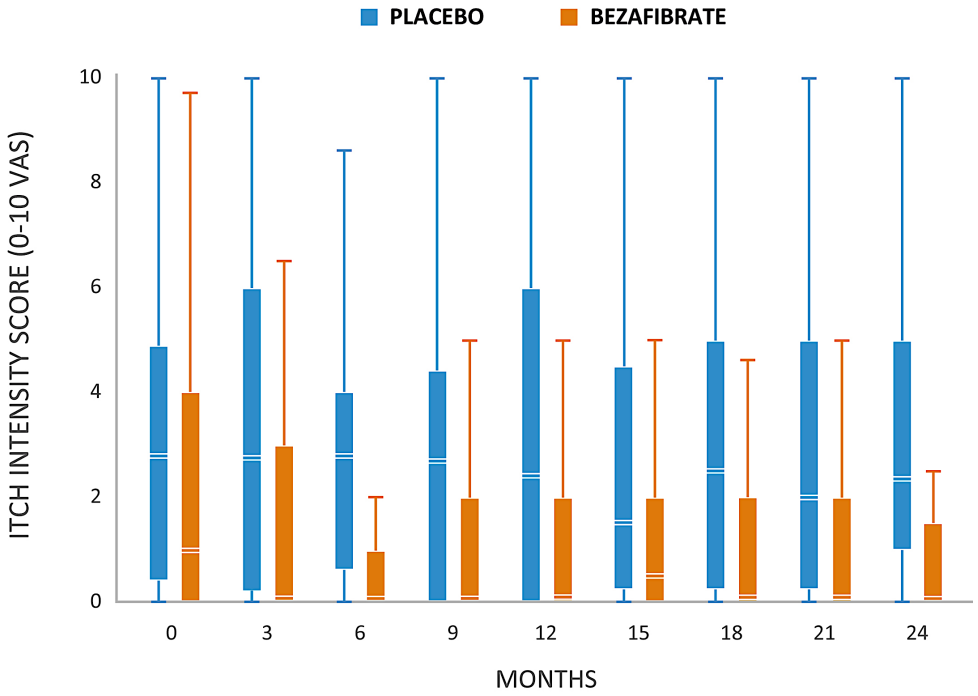


Corpechot et al. N Engl J Med 2018

CBP et Fibrates: effet sur le prurit



Reig et al. Am J Gastroenterol 2018

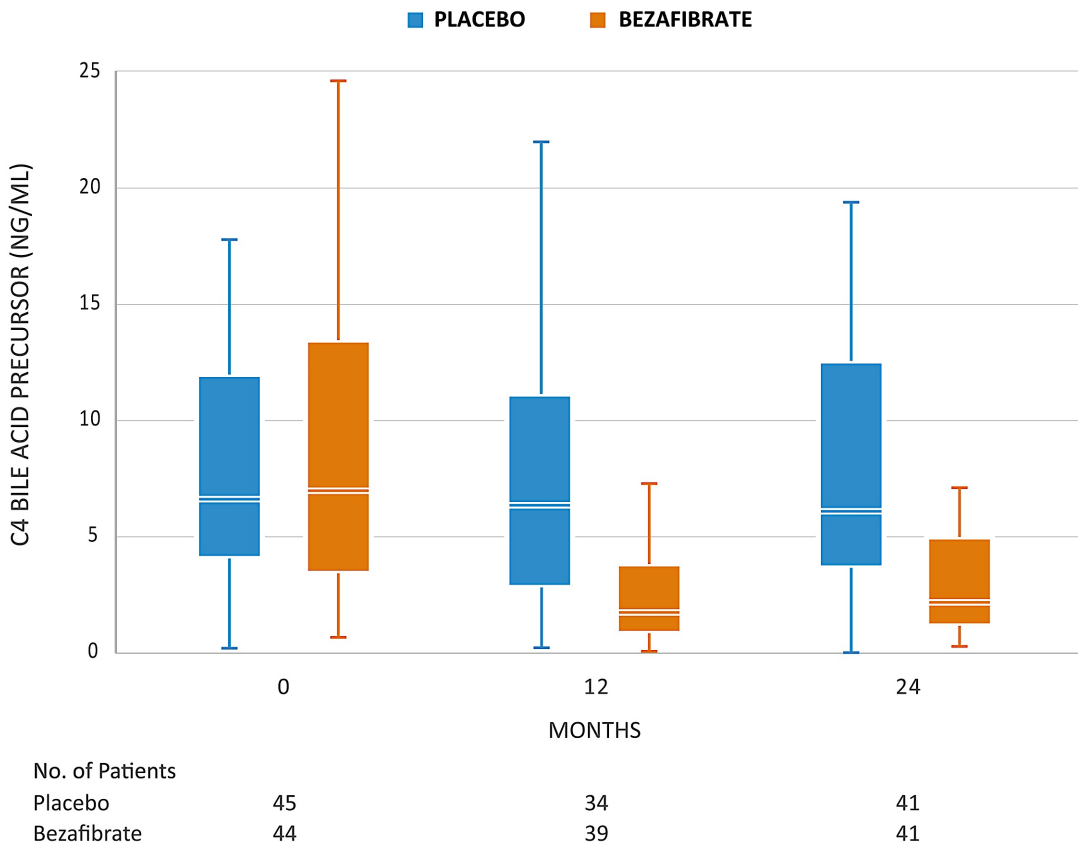


Corpechot et al. N Engl J Med 2018

Fibrates for the treatment of cholestatic itch (FITCH): NCT02701166, résultats attendus

Etude BEZURSO: effets sur les acides biliaires

Précurseur C4



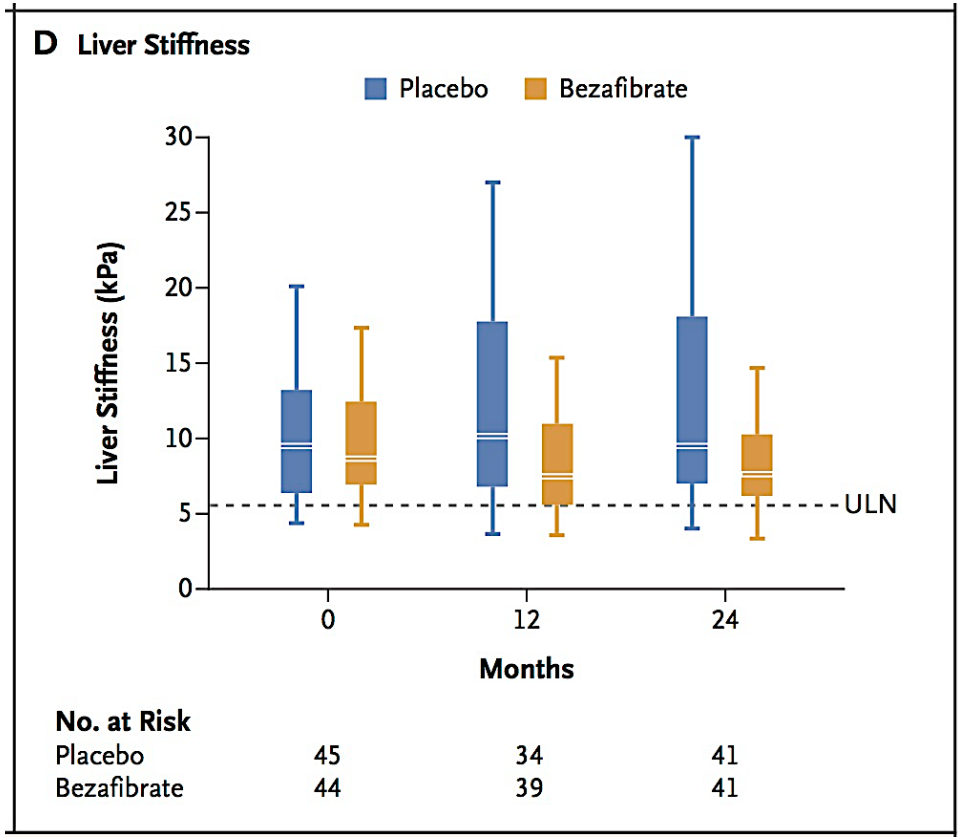
Acides biliaires endogènes

Table S12. Proportion of endogenous bile acid as assessed by linear mixed models

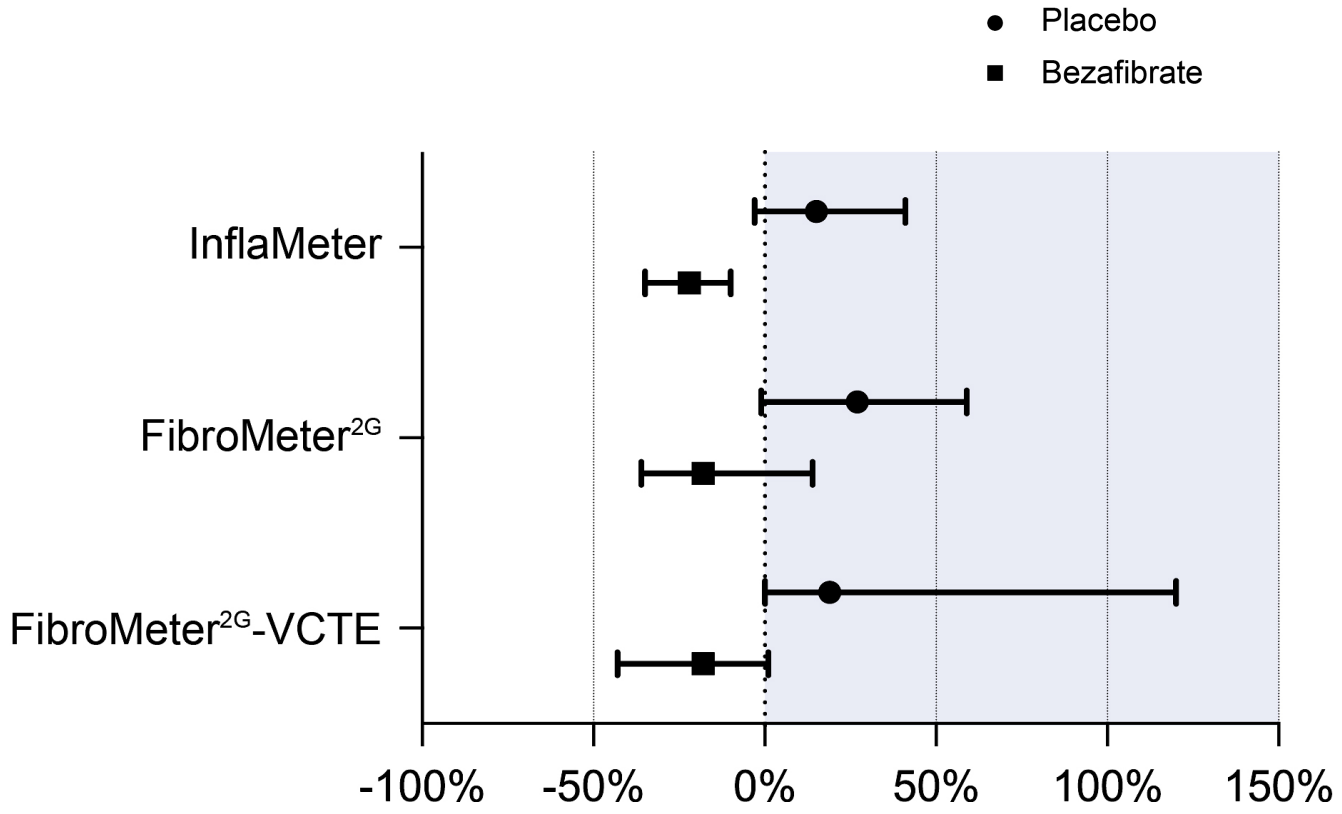
Parameter	Estimate	SE	DF	95%CI
Intercept Placebo	3.3704	0.1065	242	[3.1607 ; 3.5801]
Intercept BZF	3.4185	0.1038	242	[3.2139 ; 3.6231]
Intercept BZF vs. Placebo	0.04810	0.1487	242	[-0.2448 ; 0.3411]
Slope(time) Placebo	-0.02329	0.05036	242	[-0.1225 ; 0.07590]
Slope(time) BZF	-0.1733	0.04719	242	[-0.2663 ; -0.08035]
Slope(time) BZF vs. Placebo	**-0.1500**	**0.06901**	**242**	**[-0.2860 ; -0.01407]**

Corpechot et al. N Engl J Med 2018

Etude BEZURSO: effets sur les marqueurs de fibrose



Corpechot et al. N Engl J Med 2018



Corpechot et al. ILC 2019 (Vienna, Austria)

CBP et Fibrates: effets sur les lésions histologiques

- **Données très limitées (case reports)**
- **Essai BEZURSO:**
  - Biopsies non obligatoires
  - Analyse préliminaire sur compte-rendus de biopsie (25 couples de biopsies non centralisés, lecture non standardisée)

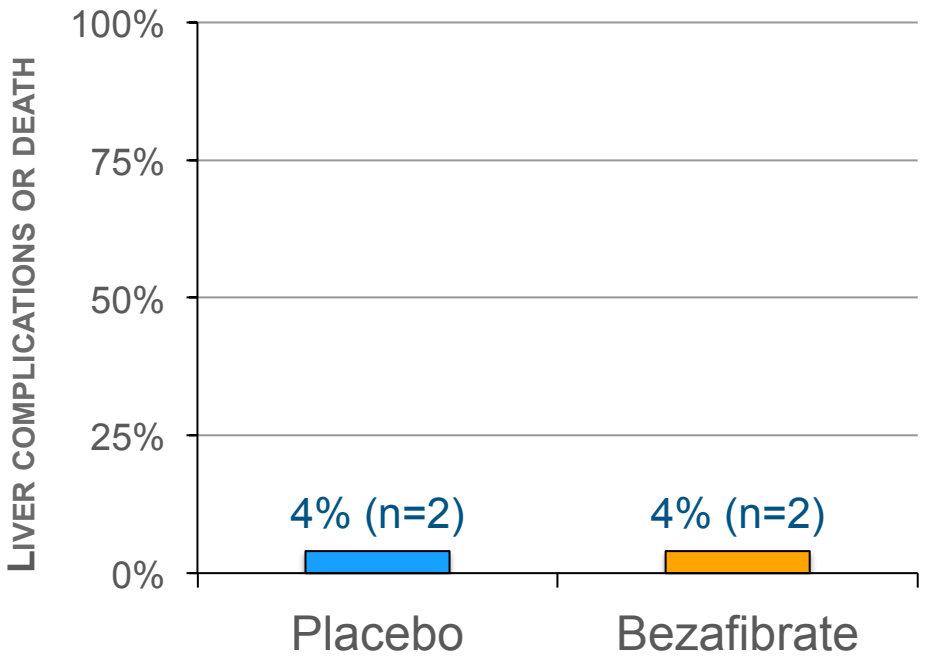
Stade histologique	Bezafibrate (n=12)	Placebo (n=13)
Amélioration	3 (25%)	2 (15%)
Stabilité	8 (67%)	6 (46%)
Aggravation	1 (8%)	5 (39%)

p=0,23

- **Etude BEZURSO-HISTOLOGY:** 32 couples de biopsies centralisés
  - Analyse morphologique standard (Pr Wendum, en cours)
  - Analyse morphométrique (programmée: été 2019, Pr Rousselet)

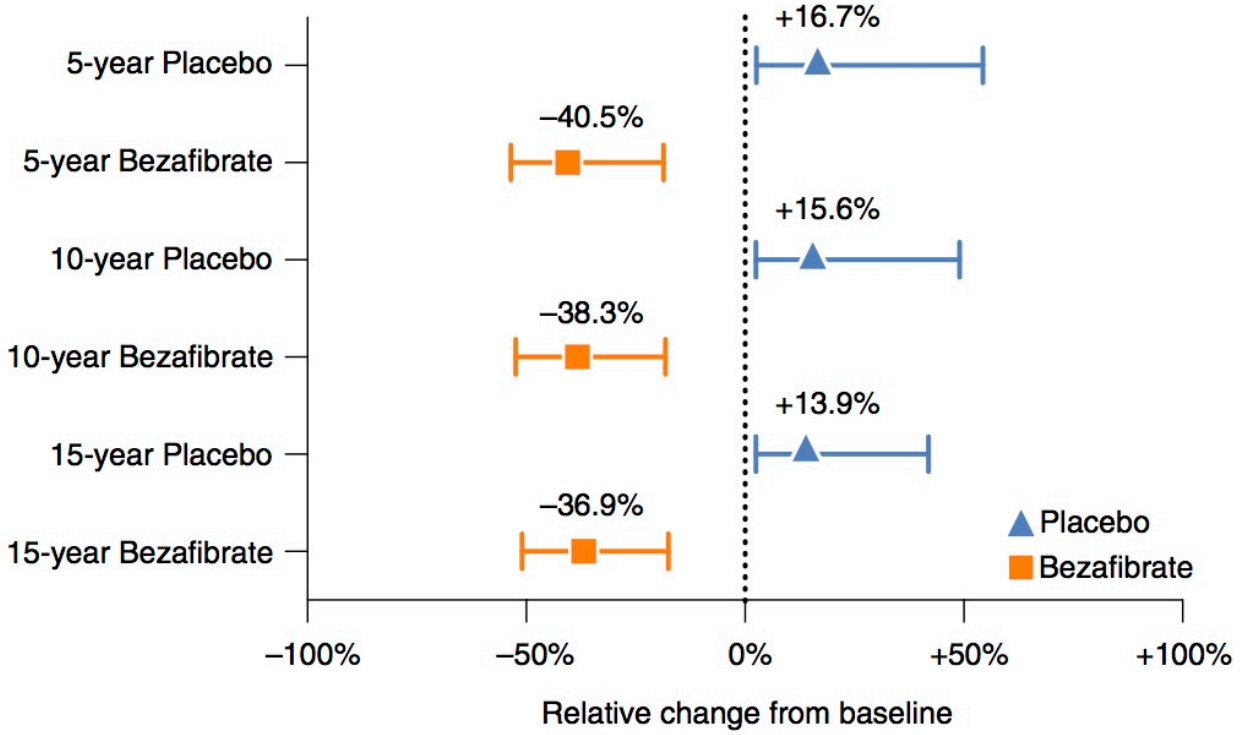
Etude BEZURSO: survie observée et prédite

Complications observées à 2 ans



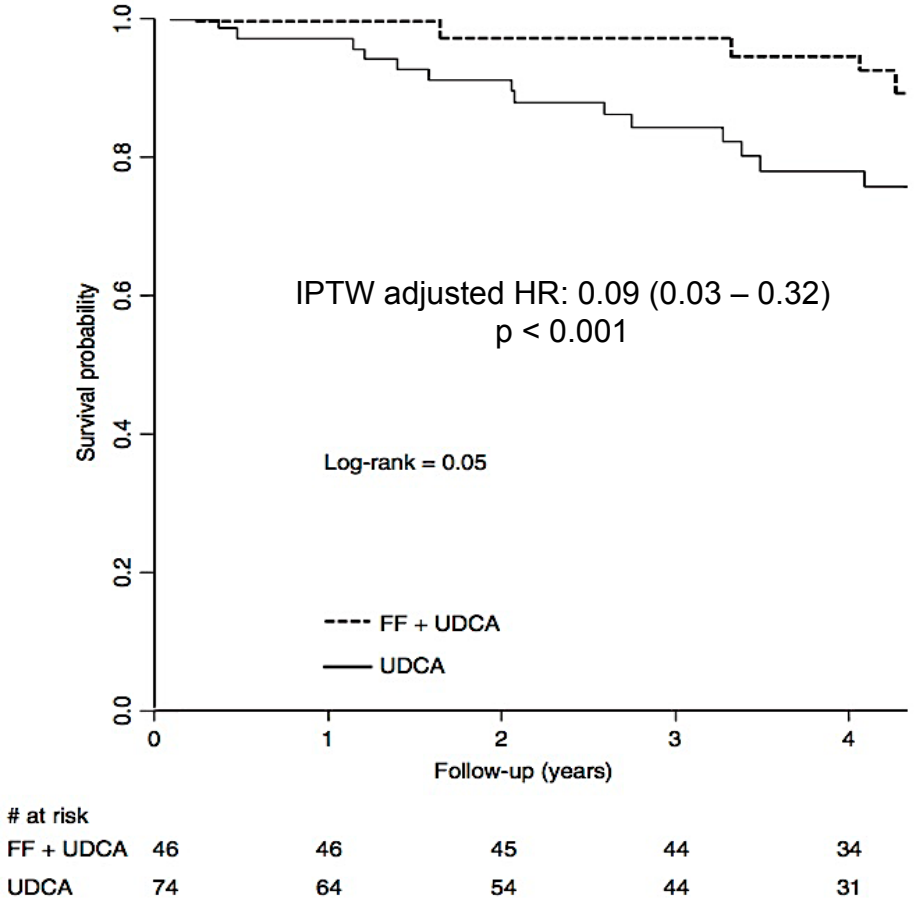
Corpechot et al. N Engl J Med 2018

Variation prédite de la mortalité / TH

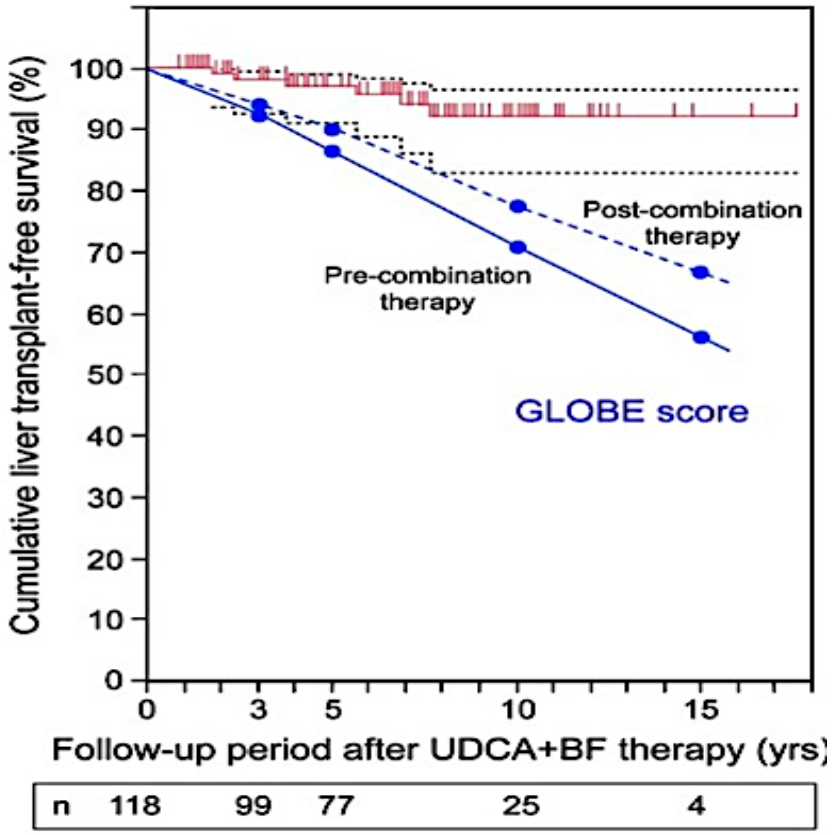


Corpechot et al. Aliment Pharmacol Ther 2019

CBP et Fibrates: effets à long terme?



Cheung et al. Aliment Pharmacol Ther 2016



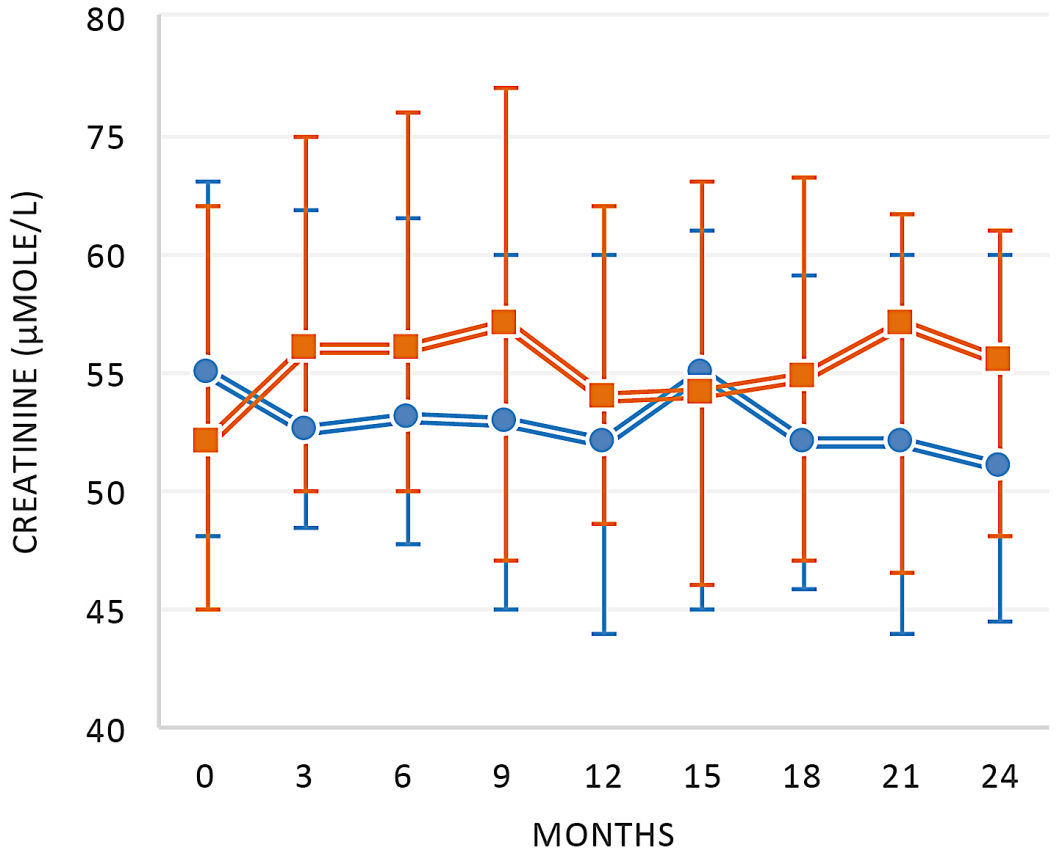
Honda et al. Hepatology 2019

Etude BEZURSO: effets indésirables

Table 3. Incidence of Adverse Events Occurring in 10% or More of Patients and All Serious Adverse Events.*

Event	Bezafibrate Group (N=50)	Placebo Group (N=50)
	no. of patients with event (%)	
Any adverse event	43 (86)	45 (90)
Arthralgia	7 (14)	11 (22)
Myalgia	10 (20)	5 (10)
Nasopharyngitis	9 (18)	10 (20)
Bronchitis	4 (8)	9 (18)
Depressive mood	7 (14)	8 (16)
Abdominal pain	7 (14)	6 (12)
Pruritus	4 (8)	7 (14)
Diarrhea	1 (2)	6 (12)
Flulike syndrome	5 (10)	5 (10)
Any serious adverse event	14 (28)	12 (24)
Aminotransferase level >5x ULN	3 (6)	1 (2)
Creatine kinase level >5x ULN	1 (2)	0
Creatinine increase with worsening stage of chronic kidney disease	1 (2)	0

↑ Créatinine (5%)



Corpechot et al. N Engl J Med 2018

Fibrates: effets indésirables (en général)

Essai FIELD (5 ans)

	Placebo (n=4900)	Fenofibrate (n=4895)
Any serious adverse event*		
Death, other than cardiovascular causes	196 (4%)	216 (4%)
Cancer	148 (3%)	168 (3%)
Respiratory disease	16 (<1%)	19 (<1%)
Trauma	12 (<1%)	11 (<1%)
Other	20 (<1%)	18 (<1%)
Non-fatal events*	3346 (68%)	3361 (69%)
Gastrointestinal	927 (19%)	975 (20%)
Cardiac	807 (17%)	727 (15%)
Musculoskeletal	739 (15%)	755 (15%)
Tumour-related†	661 (14%)	643 (13%)
Genitourinary	568 (12%)	607 (12%)
Special senses‡	527 (11%)	499 (10%)
Vascular (non-cardiac)	439 (9%)	418 (9%)
Respiratory	342 (7%)	384 (8%)
Newly diagnosed cancer	373 (8%)	393 (8%)
Colorectal	60 (1%)	67 (1%)
Prostate	59 (1%)	65 (1%)
Other gastrointestinal	49 (1%)	47 (1%)
Respiratory	41 (<1%)	45 (<1%)
Breast	38 (<1%)	37 (<1%)
Urinary	31 (<1%)	24 (<1%)
Clinically important events in <2% of patients*		
Deep-vein thrombosis	48 (1·0%)	67 (1%)
Pulmonary embolism	32 (0·7%)	53 (1%)
Pancreatitis	23 (0·5%)	40 (0·8%)
Myositis	1 (<1%)	2 (<1%)
Rhabdomyolysis	1 (<1%)	3 (<1%)
Renal disease needing dialysis	21 (<1%)	16 (<1%)
Laboratory variable measurements		
Raised alanine aminotransferase		
3–5×upper limit of normal	26 (<1%)	11 (<1%)
>5×upper limit of normal	12 (<1%)	11 (<1%)
Raised creatine phosphokinase		
5–10×upper limit of normal	7 (<1%)	11 (<1%)
>10×upper limit of normal	3 (<1%)	4 (<1%)
Raised creatinine		
>200 µmol/L	48 (1%)	73 (2%)

Data are number (%) *Other than primary and secondary cardiovascular outcomes. †Includes invasive cancers, in-situ cancers, non-melanoma skin cancers, and benign tumours. ‡Includes cataract and other eye and ear conditions.

Table 5: Clinical and laboratory evidence of safety of fenofibrate

Keech et al. Lancet 2005

Essai LEADER (5 ans)

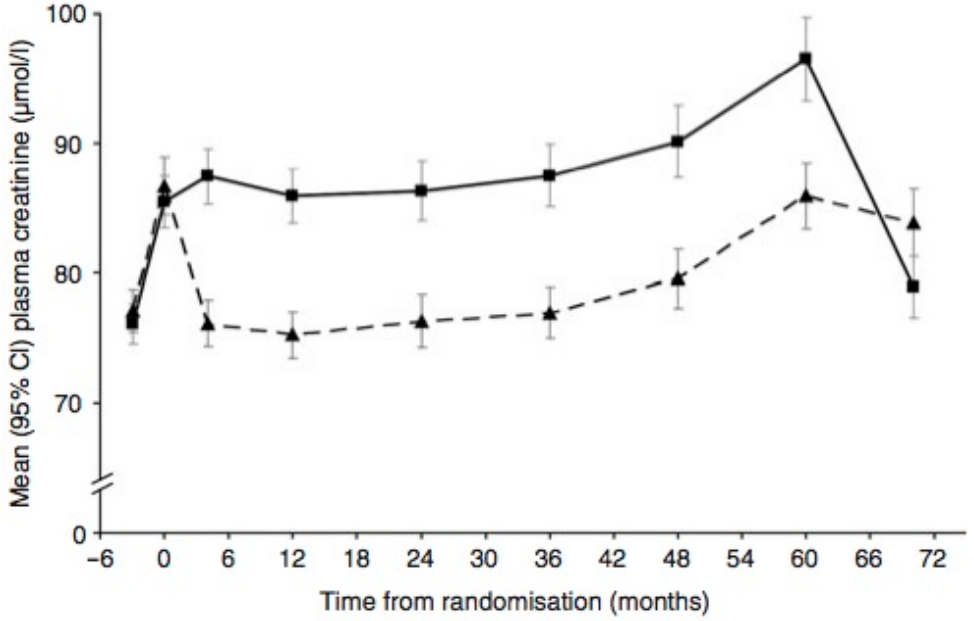
Table 3 Reasons for withdrawal from treatment. Figures are numbers (percentage) of participants

	Bezafibrate (n=783)	Placebo (n=785)	P value
Disease requiring cessation of treatment	28 (3.6)	28 (3.6)	0.99
Drug incompatible with bezafibrate	42 (5.4)	109 (13.9)	<0.0001
Excessive adverse reaction	36 (4.6)	30 (3.8)	0.44
Other relevant condition	29 (3.7)	39 (5.0)	0.22
Non-compliance	5 (0.6)	5 (0.6)	0.99
Moved away	11 (1.4)	8 (1.0)	0.49
No longer wants to participate	144 (18.4)	122 (15.5)	0.13
Other	49 (6.3)	57 (7.3)	0.43
Raised creatinine concentration	25 (3.2)	5 (0.6)	<0.0001
Total	369 (47.1)	403 (51.3)	0.10

Meade et al. BMJ 2002

Fibrates et toxicité rénale

Essai FIELD: 4895 patients traités par Fénofibrate pendant 5 ans.
Réversibilité complète de l'augmentation de la créatinine après la fin de l'étude.
Absence de complication rénale vs. placebo.



Variable	Placebo		Fenofibrate		Total	
	n[a]	%	*n*[a]	%	*n*[a]	%
Participants	4,900	100	4,895	100	9,795	100
Event						
Plasma creatinine >400 µmol/l	3	(0.1)	6	(0.1)	9	(0.1)
Renal replacement therapy	21	(0.4)	16	(0.3)	37	(0.4)
Renal transplant	0	(0.0)	0	(0.0)	0	(0.0)
Death from renal disease	4	(0.1)	1	(0.0)	5	(0.1)
Total patients with ESRD	26	(0.5)	21	(0.4)	47	(0.5)
Doubling of serum creatinine	90	(1.8)	148	(3.0)	238	(2.4)
Doubling of serum creatinine or ESRD[b,c]	103	(2.1)	152	(3.1)	255	(2.6)
Doubling of serum creatinine or ESRD[b,d]	105	(2.1)	152	(3.1)	257	(2.6)

Davis et al. Diabetologica 2011

Fibrates et toxicité musculaire

Essai FIELD (5 ans)	Placebo (n=4900)	Fenofibrate (n=4895)
Any serious adverse event*		
Death, other than cardiovascular causes	196 (4%)	216 (4%)
Cancer	148 (3%)	168 (3%)
Respiratory disease	16 (<1%)	19 (<1%)
Trauma	12 (<1%)	11 (<1%)
Other	20 (<1%)	18 (<1%)
Non-fatal events*	3346 (68%)	3361 (69%)
Gastrointestinal	927 (19%)	975 (20%)
Cardiac	807 (17%)	727 (15%)
Musculoskeletal	739 (15%)	755 (15%)
Tumour-related†	661 (14%)	643 (13%)
Genitourinary	568 (12%)	607 (12%)
Special senses‡	527 (11%)	499 (10%)
Vascular (non-cardiac)	439 (9%)	418 (9%)
Respiratory	342 (7%)	384 (8%)
Newly diagnosed cancer	373 (8%)	393 (8%)
Colorectal	60 (1%)	67 (1%)
Prostate	59 (1%)	65 (1%)
Other gastrointestinal	49 (1%)	47 (1%)
Respiratory	41 (<1%)	45 (<1%)
Breast	38 (<1%)	37 (<1%)
Urinary	31 (<1%)	24 (<1%)
Clinically important events in <2% of patients*		
Deep-vein thrombosis	48 (1·0%)	67 (1%)
Pulmonary embolism	32 (0·7%)	53 (1%)
Pancreatitis	23 (0·5%)	40 (0·8%)
Myositis	1 (<1%)	2 (<1%)
Rhabdomyolysis	1 (<1%)	3 (<1%)
Renal disease needing dialysis	21 (<1%)	16 (<1%)
Laboratory variable measurements		
Raised alanine aminotransferase		
3–5×upper limit of normal	26 (<1%)	11 (<1%)
>5×upper limit of normal	12 (<1%)	11 (<1%)
Raised creatine phosphokinase		
5–10×upper limit of normal	7 (<1%)	11 (<1%)
>10×upper limit of normal	3 (<1%)	4 (<1%)
Raised creatinine		
>200 µmol/L	48 (1%)	73 (2%)

Data are number (%) *Other than primary and secondary cardiovascular outcomes. †Includes invasive cancers, in-situ cancers, non-melanoma skin cancers, and benign tumours. ‡Includes cataract and other eye and ear conditions.

Table 5: **Clinical and laboratory evidence of safety of fenofibrate**

Keech et al. Lancet 2005

CBP	Fibrate	Myalgies (%)
Honda et al. 2019	Bezafibrate	0/118 (0%)
Corpechot et al. 2018	Bezafibrate	10/50 (20%)*
Reig et al. 2018	Bezafibrate	1/48 (2%)
Cheung et al. 2016	Fenofibrate	2/46 (4%)
Hosonuma et al. 2015	Bezafibrate	1/13 (8%)
Levy et al. 2010	Fenofibrate	0/20 (0%)
Iwasaki et al. 2008	Bezafibrate	1/12 (8%)

* 5/50 (10%) dans le groupe Placebo

Fibrates et toxicité hépatique

- Fénofibrate: 4‰ des DILI aux USA
- Cytolyse minime (<3N) transitoire: < 20%
- Cytolyse significative (>3N): < 5%
- Toxicité hépatocellulaire immuno-allergique
- Délai: quelques semaines à mois
- Auto-anticorps souvent présents (AAN, AML)
- Possible hépatite ictérique prolongée
- Réaction croisée possible entre fibrates

CBP	Fibrate	ALT > 5N (%)
Honda et al. 2019	Bezafibrate	0/118 (0%)
Corpechot et al. 2018	Bezafibrate	3/50 (6%)*
Reig et al. 2018	Bezafibrate	0/48 (0%)
Cheung et al. 2016	Fenofibrate	1/46 (2%)
Hosonuma et al. 2015	Bezafibrate	0/13 (0%)
Levy et al. 2010	Fenofibrate	0/20 (0%)
Iwasaki et al. 2008	Bezafibrate	0/12 (0%)

* 1/50 (2%) dans le groupe Placebo

Chalasani et al. Gastroenterology 2015
www.livertox.nlm.nih.gov

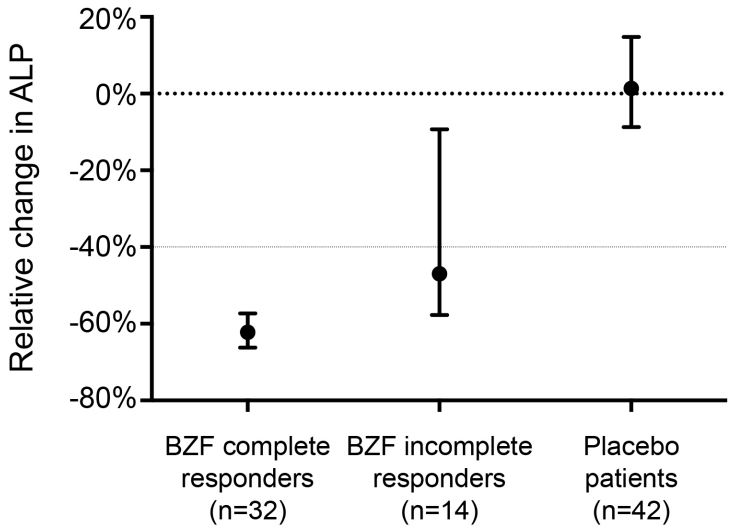
Fibrates et réponse biologique incomplète

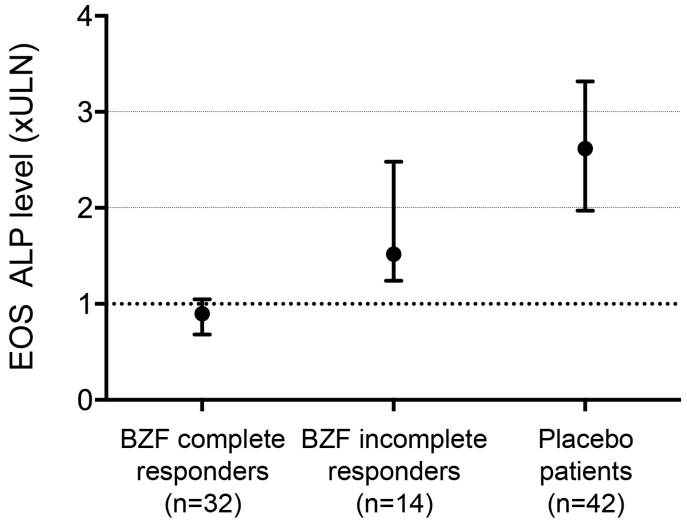
Table 1. Univariate analysis

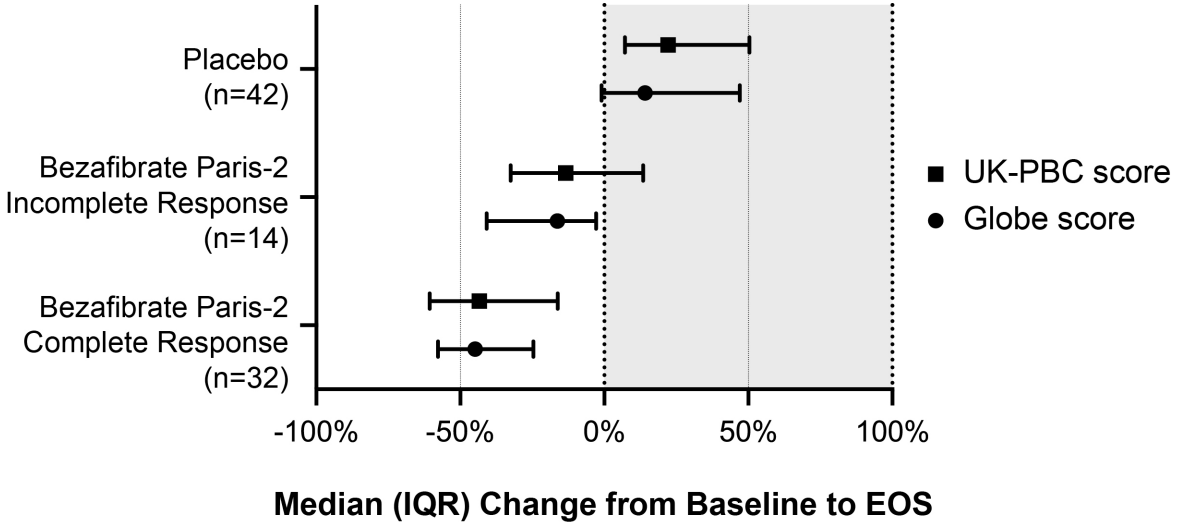
	Odds ratio [95%CI]
Portal hypertension	12.89 [1.27 - 130.55]
Itch score ≥ 3	5.83 [1.36 - 24.94]
AST – x ULN	3.96 [1.29 - 2.93]
ALP – x ULN	3.90 [1.25 - 12.22]
Bilirubin – µmole/L	1.17 [1.04 - 1.33]
Liver stiffness – kPa	1.14 [1.00 - 1.29]

Table 2. Multivariable analysis

	Odds ratio [95%CI]
Portal hypertension	15.20 [1.22 - 189.56]
Itch score ≥ 3	-
AST – x ULN	-
ALP – x ULN	4.28 [1.21 - 15.08]
Bilirubin – µmole/L	-
Liver stiffness – kPa	-

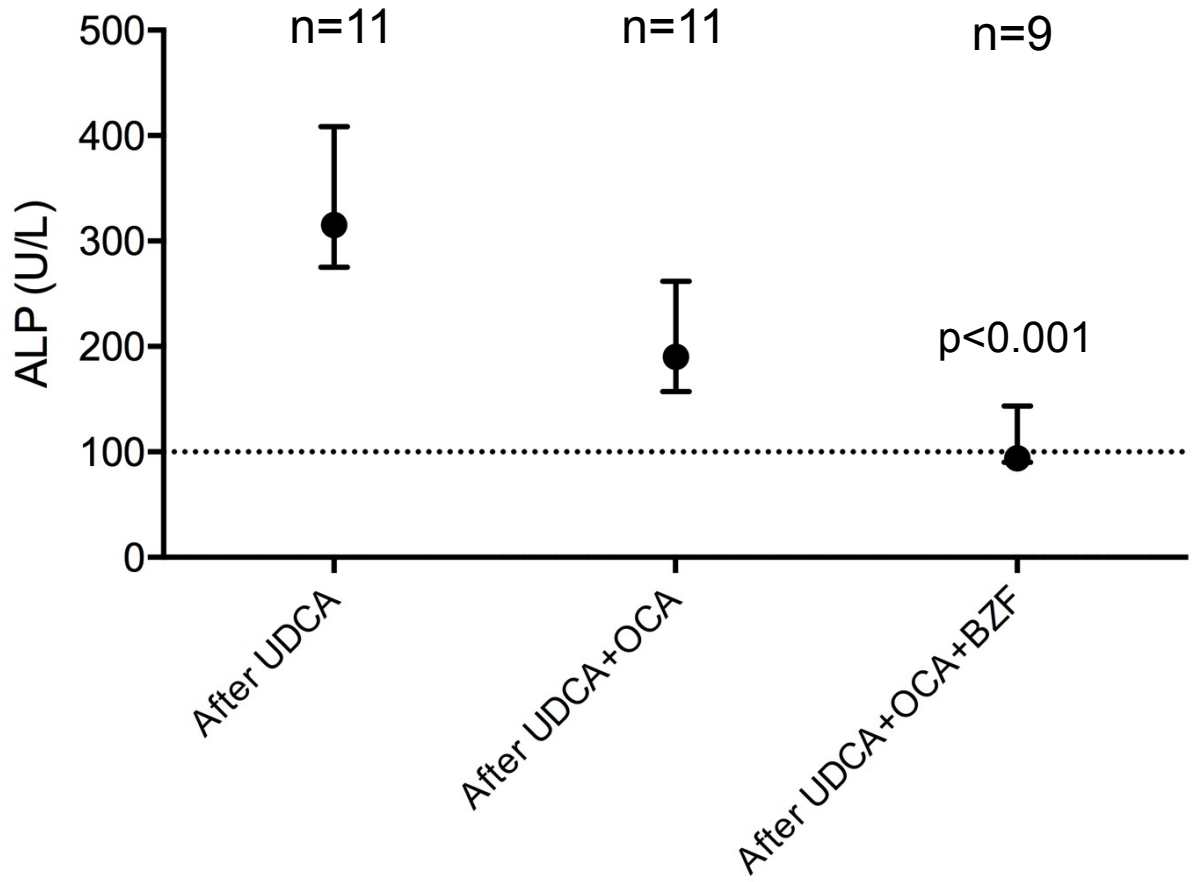






Corpechot et al. ILC 2019 (Vienna, Austria)

Fibrates + Acide Obéticholique



Normalisation des PAL 4/9
Diminution du prurit 5/7

Smets et al. ILC 2019 (Vienna, Austria)

CBP et Fibrates: en résumé

- **Les Fibrates prescrits au cours de la CBP:**
  - améliorent rapidement les marqueurs pronostiques (PAL, bilirubine)
  - diminuent les symptômes (prurit)
  - freinent l'augmentation des marqueurs de fibrose (élastométrie)
- **Leurs mécanismes d'action sont:**
  - la diminution de la synthèses des acides biliaires
  - l'augmentation de la sécrétion des phospholipides biliaires
  - un probable effet anti-inflammatoire intra-hépatique
- **Leurs principaux effets secondaires sont:**
  - les douleurs musculaires (0-20%)
  - l'augmentation modérée et réversible (5-10%) de la créatinine
  - de rares cas (<5%) d'hépatite cytolytique idiosyncrasique
- **Leur bénéfice à long terme est à démontrer concernant:**
  - la progression histologique
  - la survie sans transplantation

Conclusion

- **Actuellement en prescription hors AMM, le Bezafibrate est un traitement de 2ème intention efficace de la CBP chez les patients présentant une réponse incomplète ou une intolérance à l'AUDC.**
- **La réponse au Bezafibrate est évaluable dès le 3ème mois de traitement (PAL, bilirubine, prurit).**
- **Les transaminases, la créatinine et les CPK doivent être surveillées.**
- **Dans les pays où le Bezafibrate n'est pas disponible, le Fenofibrate est une alternative crédible.**