Bile acids drive fibroblast activation, fibrogenesis, interstitial matrix fibrosis and outcomes in PSC

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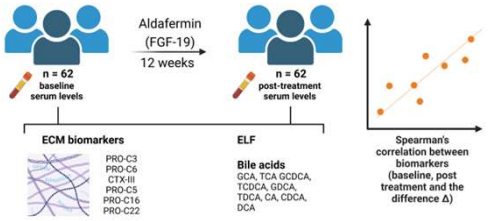
BACKGROUND

- Fibrosis often originates from a persistent insult that damages epithelial and endothelial cells and activates chronic pro-inflammatory processes that impair the regular course of tissue repair[1].
- Fibroblast activation leading to excessive production of type I, III and VI collagens in the interstitial space of the extracellular matrix (ECM) is a hallmark of fibrosis. Several drivers of fibroblast activation including TGF-β have been reported.
- Bile acids (BA) have previously demonstrated to correlate with fibroblast activation marker PRO-C3 in biliary diseases, however, their role in fibrogenesis remains unclear.

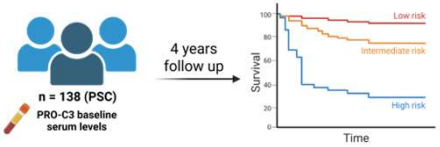
The present work aims to investigate the relationship between bile acids and markers of ECM formation and degradation during anti-fibrotic therapy (an engineered FGF-19; NCT02704364 analogue;) and related prognostic ability of biomarkers reflecting fibroblast activity in PSC.

METHODS

- ECM biomarkers of fibroblast activation (nordicPRO-C3™ and nordicPRO-C6™), fibrosis resolution (nordicCTX-III™), ECM remodeling (type VIII, XVI and XVIII collagens), the ELF score and bile acids were measured in serum from 62 patients with primary sclerosing cholangitis (PSC) at baseline (BL) and after 12 weeks treatment with Aldafermin (FGF-19) (clinical trials: NCT02704364).



- NordicPRO-C3™ (PRO-C3) was measured in serum from 138 PSC patients from a prospective study with 4 years follow up.



RESULTS

Bile acids correlate with fibroblast activation marker nordicPRO-C3™

- Strong correlations (r = 0.5) between bile acids and fibroblast activation marker PRO-C3, ECM degradation by CTX-III and the ELF score at baseline.
- Strong correlations (r = 0.62, p < 0.0001) between glycine conjugated bile acid (GCA), and fibroblast activation marker PRO-C3 at baseline[2].
- The difference between the levels post treatment with Aldafermin FGF19 and at baseline (BL), named delta (Δ), exhibited a significant correlation between GCA (ΔGCA) and PRO-C3 (ΔPRO-C3) (r = 0.33, p < 0.0001) and was borderline significant between total bile acids (ΔBA) and PRO-C3 (ΔPRO-C3) (r = 0.24, p < 0.08)[2].

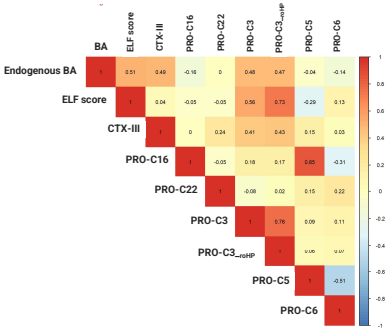


Figure 1. Spearman's correlation coefficients between bile acids and ECM biomarkers.

Table 1. Correlations between bile acids and PRO-C3 post 12 weeks treatment with aldafermin; correlations between PRO-C3 and glycine conjugated primary bile acids at baseline; and correlations between changes in bile acid levels and changes in PRO-C3 from baseline (BL) to 12 weeks post aldafermin treatment (Δ) in pooled MASH and PSC populations.

	PRO-C3 post treatment *		PRO-C3 at baseline *	
	r value	P value	r value	P value
GCA	0.62	< 0.001	0.43	< 0.001
TCA	0.52	< 0.001		
GCDCA	0.55	< 0.001	0.45	< 0.001
TCDCA	0.46	0.003		
GDCA	0.31	0.020		
TDCA	0.28	0.038		
CA	-0.18	0.18		
CDCA	-0.21	0.12		
DCA	-0.6	0.65		

* Data from literature as reported by Sanyal et al., 2021 [2]

Glycine conjugated primary bile acids

Percentage change (Δ) in bile acids from BL to week 12*	ΔPRO-C3 from BL to after treatment *	
	r value	P value
Primary Bile acids		
GCA	0.33	< 0.001
GCDCA	0.25	< 0.001
TCA	0.16	0.02
TCDCA	0.06	0.38
CA	0.23	0.001
CDCA	0.17	0.01
Secondary bile acids		
GDCA	0.34	< 0.001
TDCA	0.31	< 0.001
DCA	0.30	< 0.001
LCA	0.30	0.01

* Data from literature as reported by Sanyal et al., 2021 [2]

Fibroblast activation marker nordicPRO-C3™ for prognostic in PSC

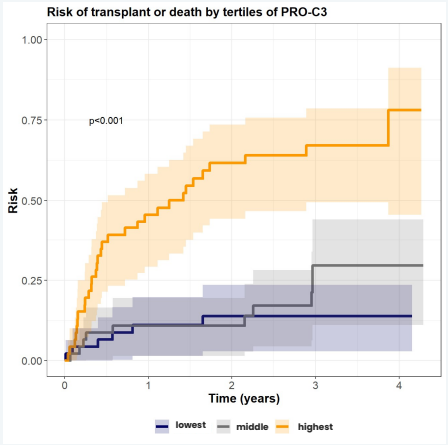


Figure 2: Kaplan-Meier curves, stratifying patients with PSC (n = 138) by tertiles of nordicPRO-C3™ (PRO-C3).

Table 2. 4-year risk and hazard ratios in PSC patients stratified according to PRO-C3 tertiles in PSC patients.

Group	Median PRO-C3	Risk [95% CI]	Hazard ratio [95% CI]
Lowest	10.8	0.14 [0.03, 0.24]	Ref.
Middle	24.8	0.30 [0.11, 0.44]	1.60 [0.58, 4.41]
Highest	67.1	0.78 [0.46, 0.91]	6.92 [2.88, 16.61]

Aldafermin therapy simultaneously reduces bile acids and PRO-C3 and the changes correlate

- PRO-C3 levels allowed to stratify PSC patients at risk of developing outcomes.
- PSC patients with higher PRO-C3 levels (upper tertile) exhibited a 5.6-fold increased risk of developing outcomes and a 7-fold increase in the hazard ratio in relation to the group with the lowest PRO-C3 levels (lower tertile).

CONCLUSIONS

- **Fibroblast activation and collagen formation are important for outcomes in PSC.**
- **The data suggest that bile acids activate fibroblast driving fibrogenesis, and that lowering of bile acids attenuate the fibrotic drive. Lowering fibroblast activity may have positive effects on liver related outcomes in PSC.**

REFERENCES

[1] Zawadzki et al., 2025. JHEP.

[2]Sanyal et al., 2021. JHEP Rep, vol 3.

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Disclosures: MK, AZ and DJL are employed at Nordic Bioscience. MK and DJL are shareholders.