Serum Bile Acids Significantly Associate with the Fibrogenesis Biomarker Pro-C3: Analysis of a Randomized, Placebo-Controlled Trial of NGM282 in Patients with Primary Sclerosing Cholangitis (PSC)

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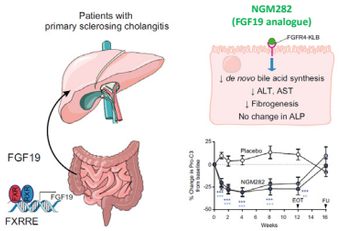
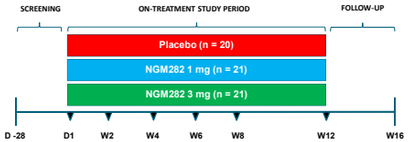
BACKGROUND AND AIMS

- Primary sclerosing cholangitis (PSC) is an inflammatory, cholestatic and progressively fibrotic liver disease devoid of effective medical interventions [1]
- NGM282 is an engineered, non-tumorigenic analogue of human FGF19 [2-3]
- NGM282 produced significant improvements in ALT, AST, and Enhanced Liver Fibrosis score (ELF), without reducing alkaline phosphatase (ALP), in a 12-week phase 2 trial in patients with PSC [4]
- In this secondary analysis, we aim to assess the impact of NGM282 on bile acid species that may be implicated in fibrosis, and to evaluate the correlation of individual bile acids with 7alpha-hydroxy-4-cholesten-3-one (C4, a marker of de novo bile acid synthesis) and Pro-C3 (a marker of fibrogenesis)



METHODS

- Sixty-two patients, with PSC by EASL criteria and an elevated ALP>1.5xULN at baseline, were randomized to NGM282 1mg, 3mg or placebo for 12 weeks [4]
- The primary endpoint was the change in ALP from baseline to Week 12 (end-of-treatment)
- Serum concentrations of individual bile acid species and C4 were determined by mass spectrometry (Mayo Clinic)
- Serum Pro-C3 was measured by an ELISA method (Nordic Bioscience)
- Continuous outcomes were analyzed with the use of a mixed-effect model repeated measures analysis of covariance
- Linear regression was used to generate straight lines for ALP with laboratory parameters; correlation coefficients between bile acids and Pro-C3 were calculated using Spearman's method

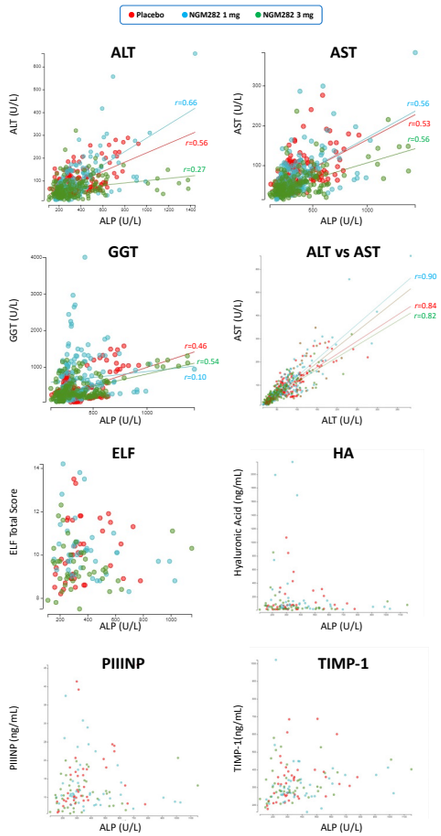


RESULTS

Correlation Between ALP and Laboratory Parameters

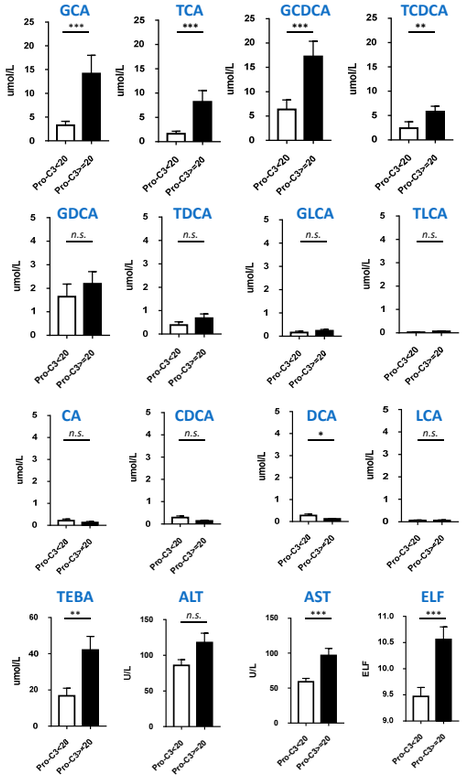
- Levels of ALP correlate with serum concentrations of ALT, AST and GGT
- Levels of ALP do NOT correlate with ELF score or its 3 components (the N-terminal pro-peptide of type III collagen [PIIINP], the tissue inhibitor of metalloproteinase 1 [TIMP-1] and hyaluronic acid [HA])

Correlation of ALP with Key Parameters



PSC Patients with Increased Fibrogenesis Had Higher Serum Bile Acids at Baseline

- We measured serum concentrations of Pro-C3, a neo-epitope of type III collagen during collagen formation reflecting true fibrogenic activity [5]
- In the current study, baseline Pro-C3 levels of ≥20 ng/mL, compared with <20 ng/mL, were associated with significantly higher levels of serum bile acids, in patients with PSC
- Given that PRO-C3 is an independent predictor of transplant-free survival in PSC [6], and that PSC patients with high baseline serum levels of Pro-C3 had shorter survival compared to patients with low baseline serum levels [6], these results suggest that bile acids may play a causative role in the increased fibrogenesis and worsened outcomes in these patients



*(***P<0.001, **P<0.01, *P<0.05; n.s., not significant)*

CA, cholic acid; CDCA, chenocholic acid; DCA, deoxycholic acid; GCA, glycocholic acid; GCDCA, glycochenocholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; LCA, lithocholic acid; TCA, taurocholic acid; TCDCA, taurochenocholic acid; TDCA, taurodeoxycholic acid; TEBA, total endogenous bile acids; TLCA, taurolithocholic acid

NGM282 Lowered Serum Bile Acids

- Serum levels of 7alpha-hydroxy-4-cholesten-3-one (C4), a marker of de novo bile acid synthesis, were significantly suppressed in the NGM282 1 mg and 3 mg groups, but not in placebo, at week 12
- Serum levels of bile acids were significantly reduced at week 12 compare to baseline in the NGM282 groups

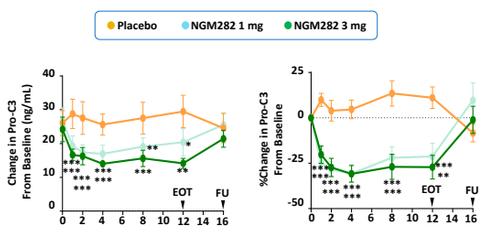
	Change from Baseline to Week 12, LS mean		
	Placebo (n=20)	NGM282 1mg (n=21)	NGM282 3mg (n=21)
Conjugated Primary Bile Acids			
GCA (µmol/L)	−3.5	−4.9***	−6.3****
TCA (µmol/L)	−0.4	−1.1	−3.4**
GCDCA (µmol/L)	−2.8	−5.8***	−5.5**
TCDCA (µmol/L)	0.1	−0.8	−2.3*
Conjugated Secondary Bile Acids			
GDCA (µmol/L)	−0.4	−1.4****	−1.6****
TDCA (µmol/L)	0.1	−0.2	−0.4*
GLCA (µmol/L)	0	−0.1*	−0.1**
TLCA (µmol/L)	0.03	−0.02	−0.03*
Unconjugated Primary Bile Acids			
CA (µmol/L)	0.1	0	0
CDCA (µmol/L)	0.1	−0.1	0.1
Unconjugated Secondary Bile Acids			
DCA (µmol/L)	0	−0.1****	−0.2****
LCA (µmol/L)	−0.01	−0.02**	−0.03***
Total endogenous bile acids			
TEBA (µmol/L)	-4.0	-12.6**	-16.8***

*(****P<0.0001, ***P<0.001, **P<0.01, *P<0.05 vs baseline)*

CA, cholic acid; CDCA, chenocholic acid; DCA, deoxycholic acid; GCA, glycocholic acid; GCDCA, glycochenocholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; LCA, lithocholic acid; TCA, taurocholic acid; TCDCA, taurochenocholic acid; TDCA, taurodeoxycholic acid; TEBA, total endogenous bile acids; TLCA, taurolithocholic acid

NGM282 Reduced Serum Pro-C3

- Both NGM282 1 mg and 3 mg doses significantly reduced serum Pro-C3 levels at all time points assessed on-treatment
- At Week 12, relative changes in Pro-C3 from baseline were −21% (P=0.008) and −27% (P<0.001) with NGM282 1mg and 3mg, respectively, versus +11% (P=0.08) with placebo



*(***P<0.001, **P<0.01, *P<0.05 vs baseline; EOT, end of treatment; FU, follow-up [4 weeks off-drug])*

Serum Bile Acids Correlate with Pro-C3

- Serum concentrations of individual bile acids, and conjugated primary bile acids in particular, significantly correlated with Pro-C3
- The lack of correlation of serum bile acids with C4 likely reflects the adaptive suppression of de novo bile acid synthesis in cholestasis in this patient population

Week 12	Pro-C3		C4	
	P value	P value	r value	P value
Conjugated primary bile acids				
GCA	0.62	<0.0001	−0.03	0.83
TCA	0.52	<0.0001	−0.12	0.37
GCDCA	0.55	<0.0001	−0.25	0.06
TCDCA	0.46	0.0003	−0.28	0.032
Conjugated secondary bile acids				
GDCA	0.31	0.020	0.27	0.038
TDCA	0.28	0.038	0.22	0.09
Unconjugated primary bile acids				
CA	−0.18	0.18	0.09	0.49
CDCA	−0.21	0.12	−0.01	0.92
Unconjugated secondary bile acids				
DCA	−0.06	0.65	0.52	<0.0001

CONCLUSION

- **Circulating concentrations of the major hydrophobic bile acids strongly correlate with the fibrosis marker Pro-C3 in PSC, suggesting that bile acids may be a molecular driver of fibrogenesis**
- **Both serum bile acids and Pro-C3 are lowered by NGM282, indicating that the effects of NGM282 on bile acid metabolism may be pathophysiologically linked to its anti-fibrotic effects in PSC**
- **Our data confirm the need for further consideration of markers such as bile acids and Pro-C3 in the determination of efficacy of new therapies for patients with PSC**

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References:

1. *Hirschfield et al., Lancet 2013; 382:1587-1599*
2. *Zhou et al., Cancer Res 2014; 74:3306-3316*
3. *Luo et al., Sci Transl Med 2014; 6:247ra100*
4. *Hirschfield et al., J Hepatol 2019; 70:483-493*
5. *Nielsen et al., Am J Transl Res 2013;5:303-315*
6. *Nielsen et al., Aliment Pharmacol Ther 2018; 48:179-189*

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Author disclosures on file at EASL 2019