Bile Acids and Liver Fibrosis: Shared Anti-Fibrotic Effects of NGM282 (Aldafermin), an FGF19 Analogue, in Primary Sclerosing Cholangitis and Non-Alcoholic Steatohepatitis

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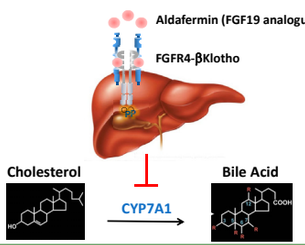
BACKGROUND

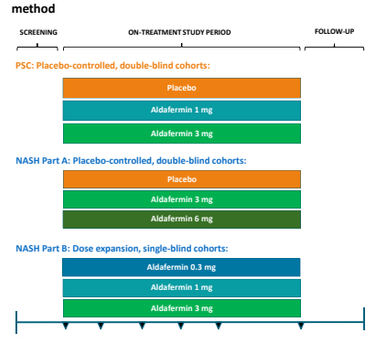
- Effective anti-fibrotic therapy for chronic inflammatory liver diseases such as primary sclerosing cholangitis (PSC) and nonalcoholic steatohepatitis (NASH) remains an unmet need for patients
- Although diseases may have distinct clinical manifestations, evidence supports a shared role of bile acid dysregulation in liver inflammation and fibrosis [1]
- Given that bile acids can cause hepatic stellate cell activation, mitochondrial dysfunction and endoplasmic reticulum stress when accumulated within hepatocytes [1], agents that reduce bile acid levels may provide an anti-fibrotic therapeutic option for patients with chronic liver disease
- NGM282 (aldafermin), a non-tumorigenic FGF19 analogue [2-4], is a potent regulator of bile acid synthesis with anti-fibrotic effect in clinical trials [5-8]
- We pooled data from phase 2 trials of aldafermin in PSC [5] and NASH [6-8] to evaluate evidence for bile acids as pro-fibrogenic triggers across cholestatic and metabolic liver disease

Aldafermin Inhibits Bile Acid Synthesis



METHODS

- 62 PSC subjects with an elevated ALP>1.5xULN at baseline (BL), received sc aldafermin 1 mg, 3 mg or placebo daily for 12 weeks (W12) [5]
- 176 NASH subjects, with NAS ≥4 (at least 1 point in each component), stage 1-3 fibrosis and absolute liver fat content by MRI-PDFF ≥8%, received aldafermin 0.3mg, 1mg, 3mg, 6mg or placebo daily for 12 weeks [6-8]
- Serum concentrations of bile acid species were determined by mass spectrometry (Mayo Clinic)
- Serum Pro-C3 (a marker of fibrogenesis) was measured by ELISA (Nordic Bioscience)
- Correlation coefficients were calculated using Spearman's method



RESULTS

Comparison of Baseline Serum Bile Acids in PSC and NASH

- At baseline, patients with PSC had markedly elevated bile acids compared to patients with NASH
- Levels of glyco- and tauro-conjugated primary and secondary bile acids were significantly higher in patients with PSC than NASH
- In contrast, unconjugated primary and secondary bile acids were lower in PSC patients

	PSC	NASH	P value
Conjugated Primary Bile Acids			
GCA (µmol/L)	8.9	0.4	<0.0001
TCA (µmol/L)	5.0	0.1	<0.0001
GCDCA (µmol/L)	12.0	1.5	<0.0001
TCDCA (µmol/L)	4.2	0.2	<0.0001
Conjugated Secondary Bile Acids			
GDCA (µmol/L)	1.9	0.9	0.0007
TDCA (µmol/L)	0.5	0.3	0.0028
Unconjugated Primary Bile Acids			
CA (µmol/L)	0.17	0.21	0.53
CDCA (µmol/L)	0.21	0.54	0.0016
Unconjugated Secondary Bile Acids			
DCA (µmol/L)	0.20	0.73	<0.0001
Total Bile Acids			
TBA (µmol/L)	66.5	5.5	<0.0001

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

- PSC patients had higher levels of ALP, ALT, AST, GGT, LDL-C, HDL-C and Pro-C3 than patients with NASH at baseline
- Plasma concentrations of triglycerides were lower in PSC patients compared with NASH patients
- ELF scores were similar between the two populations (P=0.12)

	PSC	NASH	P value
Laboratory Parameters			
ALP (U/L)	367	99	<0.0001
ALT (U/L)	102	72	<0.0001
AST (U/L)	79	55	<0.0001
GGT (U/L)	491	86	<0.0001
LDL-C (mg/dL)	131	95	<0.0001
HDL-C (mg/dL)	76	39	<0.0001
Triglycerides (mg/dL)	95	153	<0.0001
Pro-C3 (ng/mL)	26	18	0.0004

Aldafermin Lowers Serum Bile Acids Irrespective of Disease Etiology

- Administration of aldafermin produced dose-dependent reductions in bile acid species, and the more toxic, hydrophobic, glyco-conjugated bile acids in particular (e.g., GCA, GCDCA, GDCA, DCA), across both subjects with PSC or NASH
- The robust effects of aldafermin on lowering serum bile acids were independent of disease etiology

NGM282 Reduces Serum Bile Acids in Patients with PSC

Change from Baseline to Week 12

	Placebo	1 mg	3 mg
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***

***P<0.001, **P<0.01, *P<0.05 vs baseline

NGM282 Reduces Serum Bile Acids in Patients with NASH

Change from Baseline to Week 12

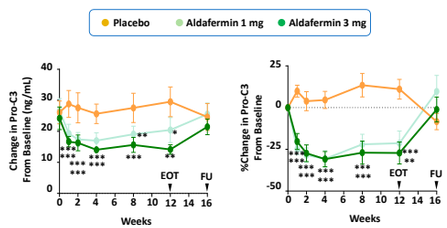
	Placebo	0.3 mg	1 mg	3 mg	6 mg
Conjugated Primary Bile Acids					
GCA (µmol/L)	0.02	−0.12*	−0.28***	−0.31***	−0.16***
TCA (µmol/L)	0.02	0.03	0	−0.05	−0.01
GCDCA (µmol/L)	−0.16	−0.36	−0.70***	−1.17***	−0.46**
TCDCA (µmol/L)	−0.01	0.12	0.09	0.04	0.12*
Conjugated Secondary Bile Acids					
GDCA (µmol/L)	−0.54	−0.25*	−0.97***	−0.64***	−0.55***
TDCA (µmol/L)	−0.08	−0.01	−0.24***	−0.18**	−0.10*
GLCA (µmol/L)	−0.01	−0.01**	−0.02**	−0.02***	−0.02***
TLCA (µmol/L)	0	0	0	0	0
Unconjugated Primary Bile Acids					
CA (µmol/L)	0.05	−0.16	−0.14	−0.23**	−0.07
CDCA (µmol/L)	0.01	−0.42**	−0.27**	−0.65***	−0.22*
Unconjugated Secondary Bile Acids					
DCA (µmol/L)	−0.05	−0.31***	−0.64***	−0.70***	−0.63***
LCA (µmol/L)	0	0	−0.01**	−0.02***	−0.02***

***P<0.001, **P<0.01, *P<0.05 vs baseline

Aldafermin Lowers Serum Pro-C3 Irrespective of Disease Etiology

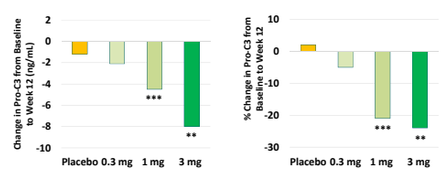
- Plasma concentrations of Pro-C3, which measures a neo-epitope of type III collagen during collagen formation and reflects fibrogenic activity [9], declined rapidly and significantly in patients with PSC or NASH after 12 weeks of aldafermin therapy
- In contrast, no significant decrease in Pro-C3 was observed in placebo-treated patients

Aldafermin Reduces Serum Pro-C3 in Patients with PSC



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

Aldafermin Reduces Serum Pro-C3 in Patients with NASH

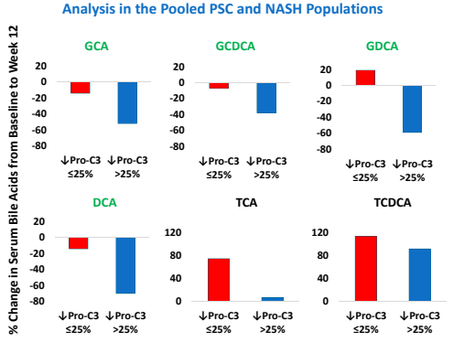


***P<0.001, **P<0.01, *P<0.05 vs baseline

Pro-C3 in Pooled PSC and NASH Populations

- Regardless of disease etiology, in pooled analysis, subjects with a fall in Pro-C3 of >25% had corresponding decreases in the toxic, hydrophobic bile acids (e.g., GCA, GCDCA, GDCA, DCA), but not TCA or TCDCA

Analysis in the Pooled PSC and NASH Populations



Correlation in Pooled PSC and NASH Populations

- In the pooled analysis (PSC and NASH populations), bile acid species strongly correlated with the fibrogenesis marker Pro-C3 at baseline and Week 12
- Percent changes from baseline to Week 12 in Pro-C3 correlated with percent changes in the toxic, hydrophobic bile acids (e.g., GCA, GCDCA, GDCA, DCA) in the pooled aldafermin trials

Correlation Between Changes in Bile Acids and Pro-C3

	Baseline		Week 12		% Change from Baseline to Week 12	
	r value	P value	r value	P value	r value	P value
Conjugated Primary Bile Acids						
GCA	0.43	<0.0001	0.47	<0.0001	0.33	<0.0001
TCA	0.43	<0.0001	0.49	<0.0001	0.16	0.02
GCDCA	0.45	<0.0001	0.49	<0.0001	0.25	0.0002
TCDCA	0.41	<0.0001	0.47	<0.0001	0.06	0.38
Conjugated Secondary Bile Acids						
GDCA	0.12	0.09	0.36	<0.0001	0.34	<0.0001
TDCA	0.14	0.04	0.41	<0.0001	0.31	<0.0001
Unconjugated Primary Bile Acids						
CA	−0.02	0.74	0.19	0.005	0.23	0.001
CDCA	−0.08	0.27	0.17	0.01	0.17	0.01
Unconjugated Secondary Bile Acids						
DCA	−0.19	0.005	0.22	0.002	0.36	<0.0001

CONCLUSION

- **Changes in circulating levels of bile acids highly correlated with changes in the fibrogenesis marker Pro-C3 in patients treated with NGM282 (aldafermin) irrespective of disease etiology**
- **Dysregulated bile acid homeostasis appears to be a shared molecular mechanism, and therapeutic target, underlying fibrosis and disease progression across cholestatic and metabolic liver disease**

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