Veillonella as a Bile Acid-Sensitive Bacteria and a Microbiome-Based Biomarker for Aldafermin (NGM282) in Patients with Non-Alcoholic Steatohepatitis

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INTRODUCTION

Recent studies have shown that the gut microbiome of elite athletes is enriched in *Veillonella*, a performance-enhancing microbe that functions via lactate metabolism [1]. *Veillonella* is selectively induced in NASH patients treated with aldafermin (previously known as NGM282), a non-tumorigenic FGF19 analogue that significantly inhibits bile acid synthesis [2-3]. We hypothesize that *Veillonella* may be a bacteria genus sensitive to bile acids. Here we assessed the correlation of *Veillonella* with bile acid species in a pooled analysis of phase 2 aldafermin trials in NASH.

AIM

- To determine the effect of aldafermin on the gut microbiota using pooled data from phase 2 studies of double-blind, placebo-controlled cohorts [4] and single-blind, dose expansion cohorts [5-6] in patients with NASH
- To correlate Veillonella abundance with individual bile acid species

METHOD

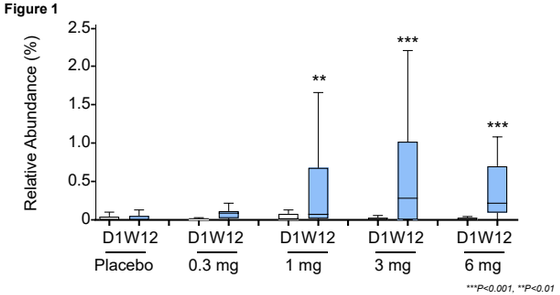
- 144 NASH subjects, with NAS ≥4 (at least 1 point in each component), stage 1-3 fibrosis and absolute liver fat content by MRI-PDFF ≥8%, received aldafermin 0.3mg, 1mg, 3mg, 6mg or placebo (PBO) daily for 12 weeks (W12), and had both baseline (Day 1) and W12 stool samples collected [4-6]
- Stool microbiota was analyzed using 16S rRNA method (Diversigen)
- Serum bile acids were measured with LC/MS (Mayo Clinic)
- We performed a linear mixed-effect model to account for non-independence of the data set with the following model: Veillonella_abundance ~ treatment_type + visit + (1|subject)
- Correlation between pre- and post-treatment in the relative abundance of *Veillonella* and bile acid species was determined using Spearman's rank correlation coefficient

RESULTS

- *Subjects treated with aldafermin had stable gut microbial composition and diversity* [2]
- *No taxonomic changes were observed among 12 phyla or the top 30 most abundant genera over time or between aldafermin and placebo, except for an increase in the low abundance genus Veillonella in subjects who received aldafermin*
- *Enrichment of Veillonella from baseline to week 12 was observed in the aldafermin groups, but not in the placebo group*

Aldafermin Enriches *Veillonella* in Patients with NASH

Figure 1



- *At W12, the appearance of Veillonella was associated with a reduction in bile acid levels*
- *The relative abundance of Veillonella was negatively correlated with concentrations of bile acids, and the more hydrophobic, toxic bile acids in particular*

Figure 2

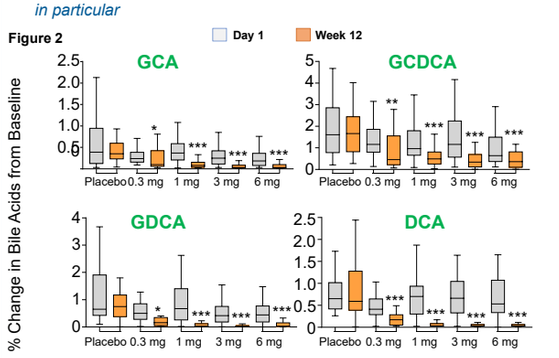
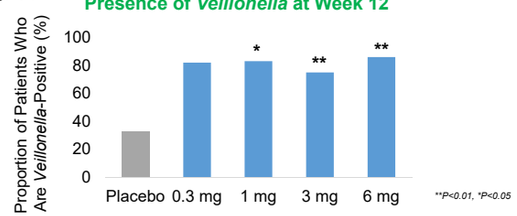


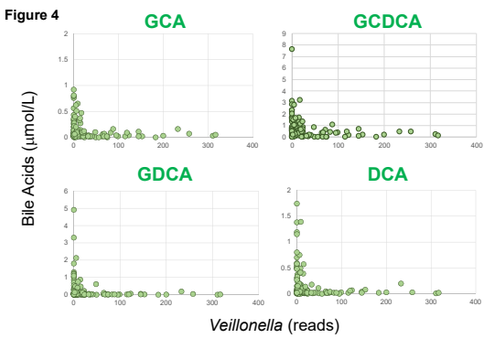
Figure 3

Presence of *Veillonella* at Week 12



Correlation Between *Veillonella* and Bile Acids at Week 12

Figure 4



Correlation of Bile Acid Species and *Veillonella* at Week 12

Table 1

Bile Acid Species	*rho*	P
GCA	**– 0.37**	**<0.0001**
GCDCA	**– 0.38**	**<0.0001**
TCA	– 0.24	0.01
TCDCA	– 0.11	0.25
GDCA	**– 0.45**	**<0.0001**
TDCA	**– 0.36**	**<0.0001**
GLCA	**– 0.30**	**0.001**
TLCA	– 0.15	0.11
CA	– 0.20	0.03
CDCA	– 0.17	0.07
DCA	**– 0.38**	**<0.0001**
LCA	– 0.27	0.003

CONCLUSIONS

- Through a large scale, hypothesis-free, stool microbiome profiling, we have identified *Veillonella* as a sensitive gut microbiome marker of aldafermin therapy in patients with NASH
- The lactate-consuming *Veillonella* appear to be sensitive to bile acids, and correlate with concentrations of the more hydrophobic, toxic bile acid species
- Given that levels of lactate are elevated in patients with cirrhosis and predict organ failure and mortality, the ability of aldafermin to enrich lactate-degrading *Veillonella* in the gut could have a protective effect in advanced liver disease

ACKNOWLEDGEMENTS

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REFERENCES

1. **Scheiman et al.,** Meta-omics analysis of elite athletes identifies a performance-enhancing microbe that functions via lactate metabolism. *Nat Med 2019;25:1104.*

2. **Sanyal et al.,** Stable gut microbiome composition and diversity with NGM282 (Aldafermin) therapy in patients with non-alcoholic steatohepatitis. *AASLD 2019 – The Liver Meeting 2019 – Boston, United States.*

3. **Zhou et al.,** Separating tumorigenicity from bile acid regulatory activity for endocrine hormone FGF19. *Cancer Res 2014;74:3306-16.*

4. **Harrison et al.,** NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet 2018;391:1174-1185.*

5. **Rinella et al.,** Rosuvastatin improves the FGF19 analogue NGM282-associated lipid changes in patients with non-alcoholic steatohepatitis. *J Hepatol 2019;70:735-744.*

6. **Harrison et al.,** NGM282 improves liver fibrosis and histology in 12 weeks in patients with nonalcoholic steatohepatitis. *Hepatology 2019 Feb 25. doi: 10.1002/hep.30590.*

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