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 MRS-PDFF 28%, received aldafermin 0.3 mg, 1 mg, 3 mg or placebo (PRO) daily for 12 weeks (W12), and had both baseline (Day 1) and W12 stool samples collected 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 4.
• No taxonomic changes were observed among 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.

• 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 acid species in particular

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

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REFERENCES