Stable Gut Microbiome Composition and Diversity with NGM282 (Aldafermin) Therapy in Patients with Non-alcoholic Steatohepatitis

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INTRODUCTION

The composition of the human gut microbiota is linked to health and disease 1, and knowledge of the impact of therapeutics on the microbiota is essential to decipher their pharmacologic activity. Aldafermin, a non-tumorigenic FGF19 analogue, significantly inhibited bile acid synthesis, reduced steatosis, and improved insulin sensitivity in patients with non-alcoholic steatohepatitis (NASH). Here we report the effect of aldfermin on the gut microbiota of patients in a phase 2 study of double-blind, placebo-controlled cohorts 2-6 and expanded cohorts 4 and 5 in patients with NASH.

RESULTS

Alpha Diversity

- 85% of reads produced were mapped to the SGH database
- Microbial richness and evenness were measured by alpha diversity
- No change in relative abundance of Bacteroidetes, Firmicutes, Actinobacteria, Fusobacteria, Tenericutes, Cyanobacteria, Lentisphaerae, Synergistetes, Euryarchaeota and Spirochaetae
- Among all taxa in the study groups, a low abundance bacterial genus, Veillonella, was the only type exhibiting significant differences between groups.

Phylum Level

- There were no significant differences in the abundances of main phyla in the groups analyzed.
- No change in the relative abundance of Erysipelotrichidae, Firmicutes, Proteobacteria, Verrucomicrobia, Actinobacteria, Arcomanobacteria, Lentisphaerae, Synergistetes, Euryarchaeota and Spirochaetae

Genus Level

- There were no significant differences in the abundances of the top 20 most-abundant genera or groups of Veillonella and placebo.
- GAM analysis revealed that age was a factor in differences between time points in the study groups.

Stable Gut Microbiome by Alpha Diversity in Patients Treated with Aldafermin

Stable Gut Microbiome by Beta Diversity in Patients Treated with Aldafermin

Phylogenetic trees with taxonomic classification using Ribosomal数据库

METHODS

144 NASH patients, with NGM 0-6 (at least 1 point in each component), stage 1-3 fibrosis and alcohol-free for 1 year, were treated with 0.3 mg, 1 mg, and 3 mg doses of aldfermin daily for 12 weeks (W12), and had both baseline (W0) and W12 stool samples collected. Samples were extracted and sequenced using the 16S v4 region at Diversigen (Houston, TX). We compared pre- and post-treatment in alpha diversity, beta diversity and taxonomy. A principal coordinates analysis was used to show differences between groups. P values were calculated using Friedman-Whitney or Mann-Whitney tests with Benjamini-Hochberg false discovery rate correction. A general linear model (GLM) was used to incorporate additional covariates.

CONCLUSION

- Enrichment of Veillonella is a biomarker for NASH and NGM282 therapy increases the abundance of Veillonella in the gut microbeoome in 12 weeks in patients with NASH.
- Enrichment of Veillonella and aldfermin therapy increases the abundance of Veillonella in the gut microbeoome in 12 weeks in patients with NASH.
- Subjects who received aldfermin, but not placebo, had a statistically significant increase from baseline in the relative abundance of Veillonella at Week 12.
- Recent studies have identified a link between members of the genus Veillonella and exercise performance 7, 8. These findings suggest that the induction of Veillonella represents a natural, microbiome-encoded enzymatic process that enhances athletic performance.
- Through this large scale, hypothesis-free, stool microbiome profiling effort, we have identified Veillonella as a sensitive gut microbiome marker of aldfermin therapy in patients with NASH.
- The role of Veillonella in lactate metabolism and its enrichment in “athletic gut microbiome” may have important implications for aldfermin therapy.

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