The FGF19 Analogue Aldafermin Enriches the Lactate-Consuming, Bile Acid-Sensitive Commensal Microbe *Veillonella* in Patients with Primary Sclerosing Cholangitis

Ulrich Beuers [1], Lei Ling [2], Duy M. Dinh [3], Hsiao D. Lieu [2], Alex M. DePaoli [2], Rohit Loomba [4], Gideon Hirschfield [5]

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INTRODUCTION

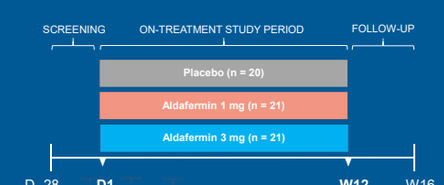
- Primary sclerosing cholangitis (PSC) is a rare, chronic cholestatic liver disease characterized by inflammation and fibrosis of intra- and extra-hepatic bile ducts [1]
- Intestinal dysbiosis has been implicated in the pathogenesis of PSC [2]
- Emerging evidence suggests that alterations in bile acids and the microbiome may contribute to the risk and progression of PSC [2]
- Aldafermin, a non-tumorigenic FGF19 analogue, suppressed bile acid synthesis and decreased hepatic inflammation and fibrosis markers, without affecting alkaline phosphatase levels, in a randomized, double-blind, placebo-controlled phase 2 study in patients with PSC [3]
- Here we report results of aldafermin on the gut microbiota from this study

AIM

To evaluate change in the gut microbiome in a randomized, double-blind, placebo-controlled study of aldafermin in patients with PSC

METHOD

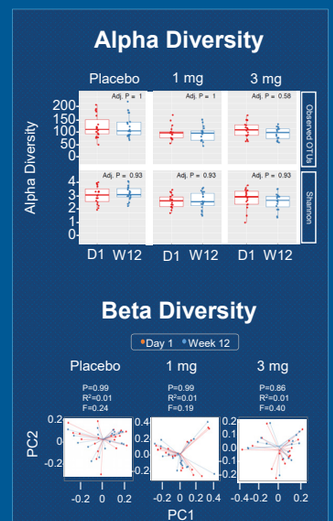
- 62 subjects, with PSC by EASL criteria and an elevated ALP>1.5xULN at baseline, were randomized to daily aldafermin 1 mg, 3 mg or placebo for 12 weeks [3]
- Stool samples were collected at baseline (BL) and week 12 (W12), extracted, and sequenced in the 16S rDNA V4 region on the MiSeq platform
- Serum bile acids were measured by mass spectrometry method
- We compared gut microbiome pre- and post-treatment in alpha diversity, beta diversity and taxonomy
- A principal coordinate analysis was used to show differences between groups
- P values were calculated using Kruskal-Wallis or Mann Whitney tests with Benjamini-Hochberg false discovery rate correction

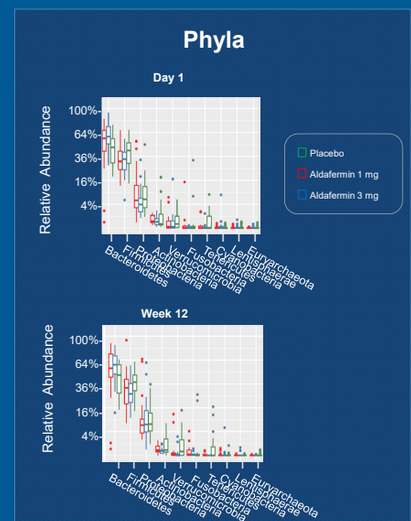


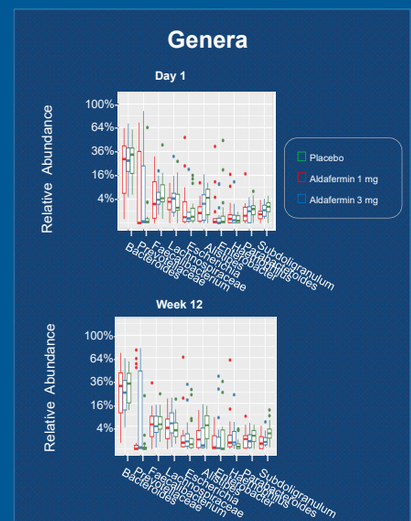
RESULTS

- *81% of reads produced were mapped to the SILVA(v4) database*
- *There were no differences in alpha diversity for each treatment group at baseline or week 12*
- *UniFrac-based principal coordinates analysis did not reveal any clustering in treatment groups by time*
- *No changes were observed among top phyla (Bacteroidetes, Firmicutes, Proteobacteria, Fusobacteria, Actinobacteria, Tenericutes, Verrucomicrobia, Cyanobacteria, Euryarchaeota, Lentisphaerae, Deferribacteres and Synergistetes) over time or between aldafermin and placebo*
- *No changes were observed among the top 30 most abundant genera over time or between aldafermin and placebo.*
- *Aldafermin treatment enriched a rare genus Veillonella at week 12*
- *The abundance of Veillonella was inversely correlated with deoxycholic acid (DCA), suggesting that Veillonella may be sensitive to bile acids, and hydrophobic bile acids in particular*

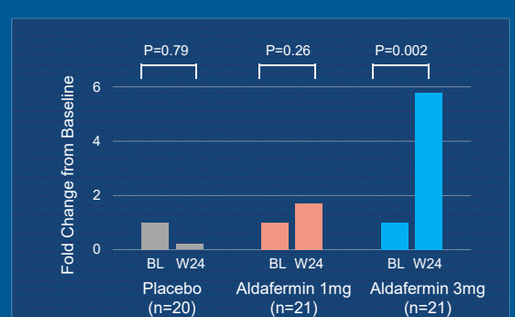
Stable Microbiome in Patients Treated with Aldafermin





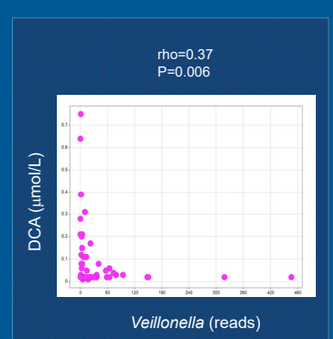


Aldafermin Enriched *Veillonella*



Subjects who received aldafermin, but not placebo, had a statistically significant increase from baseline in the relative abundance of a rare genus Veillonella at week 12 (1.7- and 5.8-fold increase in the 1 mg and 3 mg groups, respectively, vs no increase in the placebo group).

Veillonella Inversely Correlated with DCA



Veillonella abundance was inversely correlated with deoxycholic acid (DCA) at week 12 (Spearman's method).

CONCLUSIONS

- PSC patients treated with aldafermin had stable gut microbial composition and diversity
- No taxonomic differences were observed except for an increase in the rare genus *Veillonella*, a commensal microbe known to have lactate-degrading and performance-enhancing properties [4]
- These results echo our previous findings in non-alcoholic steatohepatitis [5], suggesting that *Veillonella* may serve as a microbiome-based marker for response to aldafermin irrespective of disease etiology

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Author Affiliations

1University Medical Centres, Location AMC, The Netherlands; 2NGM Biopharmaceuticals, US; 3Diversigen Inc., US; 4University of California, San Diego, US; 5Toronto Centre for Liver Disease, University Health Network, University of Toronto, Canada

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