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

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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. Intestinal dysbiosis has been implicated in the pathogenesis of PSC. Emerging evidence suggests that alterations in bile acids and the microbiome may contribute to the risk and progression of PSC.

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.

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.
• 50 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, Bacteroidia, Lentisphaerae, Deinococcus-cateniformes, Deinococcales and Synergistales) over time or between aldafermin and placebo.
• No changes were observed among the top 35 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.

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.
• These results echo our previous findings in non-alcoholic steatohepatitis, suggesting that Veillonella may serve as a microbiome-based marker for response to aldafermin irrespective of disease etiology.

REFERENCES


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SCREENING

ON-TREATMENT STUDY PERIOD

FOLLOW-UP

D-28
D1
W12
W16

Aldafermin 1 mg (n=21)
Aldafermin 3 mg (n=21)
Placebo (n=20)
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).

CONCLUSIONS

Aldafermin Enriched Veillonella

Veillonella Inversely Correlated with DCA

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

Stable Microbiome in Patients Treated with Aldafermin

Alpha Diversity

Beta Diversity

Phyla

Genera

Week 12

Day 1

CONCLUSIONS

CONCLUSIONS

REFERENCES