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

- Primary sclerosing cholangitis (PSC) is a rare, chronic cholestatic liver disease characterized by inflammation and fibrosis of intra- and extra-hepatic bile ducts.

- 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.

**Population:**
- PSC
- ALP >1.5xULN

**Trial Timeline:**
- Screening
- On-treatment study period
- Follow-up

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

Beuers et al., Abstract 1074 (EASL 2021)

1Dyson et al., Lancet 2018; 391: 2547–59; 2Hirschfield et al., J Hepatol 2019;70:483-493
Stable Microbiome in PSC Patients Treated with Aldafermin

Alpha Diversity

- No changes were observed among all phyla over time or between aldafermin and placebo
- No changes among the top 30 most abundant genera over time or between aldafermin and placebo
Aldafermin Enriched a Rare Genus *Veillonella*

**Veillonella Abundance**

- Placebo (n=20): P=0.79
- Aldafermin 1mg (n=21): P=0.26
- Aldafermin 3mg (n=21): P=0.002

- The relative abundance of *Veillonella* increased by 1.7- and 5.8-fold in the aldafermin 1 mg and 3 mg groups, respectively, vs no increase in the placebo group.

**Correlation Between Veillonella and DCA**

- *Veillonella* inversely correlated with DCA at week 12.
  - rho=0.37, P=0.006

Beuers et al., Abstract 1074 (EASL 2021)
Veillonella is a Lactate-Consuming Commensal Microbe Associated with Performance in Athletes

Meta-omics analysis of elite athletes identifies a performance-enhancing microbe that functions via lactate metabolism

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• Previous studies in non-alcoholic steatohepatitis also revealed an enrichment in Veillonella with aldafermin

Conclusion

• 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

Acknowledgment

• We thank all of the patients who participated in this study, and the investigators, study coordinators and staff for their support