Secondary bile acid production by a diverse commensal flora may be a critical factor in preventing recurrence of Clostridioides difficile infection (CDI). Key enzymes involved are bacterial-encoded bile salt hydrolases (BSHs), felt to be “gatekeepers” to secondary bile acid synthesis. Ridinilazole, a novel narrow spectrum drug for CDI, demonstrated superior sustained clinical response compared to vancomycin in Phase 2. Longitudinal sampling during this trial allowed for assessment of metabolites differentially present in stools during/after therapy with either broad or narrow spectrum anti-CDI agent. Previous work characterizing subject’s fecal microbiota in this trial showed that unlike vancomycin, ridinilazole has little effect on commensal flora during and after therapy. We hypothesized that ridinilazole’s microbiota-preserving effect is associated with lack of accumulation of conjugated primary bile acids and/or reaccumulation/persistence of secondary bile acids over the course of CDI treatment, when compared with vancomycin-treated subjects. Further, we hypothesized that we would observe correlations between treatment arms and predicted BSH gene abundances.

METHODS

Sequential stool samples were obtained from 44 subjects treated with either ridinilazole or vancomycin (22 in each arm), ranging in time from CDI diagnosis, at end-of-therapy, and up to 40 days after diagnosis. Bile acids were quantitated by liquid chromatography-mass spectrometry. Using the PICRUSt algorithm, metagenomic predictions of BSH gene abundances were performed using previously determined microbiota profiles. Control stool samples (n=31) were obtained from age-, gender- and location-similar volunteers enrolled in a separate study, and extracted similarly as the samples from CDI subjects in this study.

RESULTS

For both treatment groups, the log fold change in the indicated bile acid groups from baseline to subsequent time points was calculated for each individual subject, then averaged. Data shown are mean +/- SEM. Panel A: BSH gene abundance predicted by PICRUSt at end-of-therapy. **=P<0.001 by Wilcoxon rank sum test. Panel B:  Relationship between log10(conjugated/secondary BA) and predicted BSH gene abundances are higher in ridinilazole-treated subjects and correlated with the ratio of conjugated to secondary bile acids.

CONCLUSIONS AND FUTURE DIRECTIONS

Conclusions: In contrast to vancomycin, ridinilazole treatment preserves bile acid composition over the course of therapy. Because bile acid homeostasis affects C difficile germination and growth, this effect may have contributed to ridinilazole’s higher rate of sustained clinical response in the Phase 2 trial.

Future work:
- Explore correlations between specific taxa and bile acid composition.
- Assess bile acid features at end-of-treatment, predictive of recurrence (e.g., secondary, conj:sec) and other metabolites that may be differentially present between times/Treatments.

DISCLOSURES

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