Ridinilazole Reduces Recurrence of Clostridium difficile Infection with Minimal Impact on the Gut Microbiota

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Introduction

• C. difficile infection (CDI) is one of 3 urgent antibiotic-resistant bacterial threats in the U. S., according to the CDC, and is the leading cause of hospital-acquired diarrhea.
• A major clinical challenge is the high risk of recurrence (up to 35% following initial infection), with dysbiosis of the gut microbiome.
• Ridinilazole (RDZ) is a novel, oral, peripherally restricted antibacterial that is highly selective for C. difficile
• RDZ has shown superior efficacy on Sustained Clinical Response (SCR) compared to vancomycin (VAN) in a Phase 2 clinical trial and preservation of the gut microbiota.

Methods

• In vitro Susceptibility: MICs were determined by agar dilution on Wilkins-Chalgren plates, or, following the CLSI M11-A7/A8 for C. difficile, and, the CLSI M11-A8 and MT-A9 for the panel of bacteria.
• Multi-center, Double-blind Phase 2 Clinical Trial: 100 subjects were randomized 1:1 to RDZ (200 mg BID) or VAN (125 mg QID) treatment for 10 days. Primary endpoint was SCR, defined as clinical response at end of therapy (EOT) with no recurrence for 30 days.
• Microbiome: Stool samples from 22 patients in each treatment arm were collected at baseline and EOT. Amplicons of the 16S rRNA V4 region were analysed to identify the differences in microbiota composition at the 2 time-points using QIIME and LEfSe.

Results: Clinical efficacy

• RDZ showed limited activity against Gram-positive and Gram-negative anaerobes, especially against the Bacteroidetes, a dominant phylum of the gut microbiome.

Results: Gut Microbiome

• Vancomycin treatment resulted in dramatic losses in Bacteroidetes (>3log), in 4 families of the Firmicutes, including the Lachnospiraceae and Ruminococcaceae (>2 log), and in Actinobacteria (70% reduction). Simultaneously, an increase in Proteobacteria was observed, primarily in Enterobacteriacae (> 2 log).
• In contrast, ridinilazole’s effect was confined to the Firmicutes, with loss of C. difficile and modest decreases in the Clostridiaceae and Ruminococcaceae.

Conclusions

• Ridinilazole demonstrated potent activity against C. difficile clinical isolates with no major variation by geographic region, ribotype or antibiotic resistance phenotype.
• Ridinilazole effectively targets C. difficile in CDI patients with minimal impact on the gut microbiota.
• Preservation of the microbiome likely contributed to the low rate of recurrence, and superior efficacy on SCR, compared to vancomycin.
• These data provide evidence of ridinilazole being a microbiome sparing agent to both treat CDI and reduce the recurrence of CDI. Further clinical development is warranted.