Cnazolid Activity against Contemporary Antibiotic-resistant Cl. difficile Isolates and Prevalent Ribotypes from Europe

INTRODUCTION

- **C. difficile** has been a leading cause of nosocomial diarrhea worldwide.
- Hypervirulent **C. difficile** strains, such as ribotypes 027 and 078 have emerged which display increased resistance to a number of antibiotics and produce binary toxin in addition to toxin A and B (1). Infection caused by these strains has been associated with increased disease severity and mortality (2).
- Cadazolid is a novel antibiotic which combines quinolone and oxazolidinone moieties into a new class of antibacterial agents referred to here as quinoxolidinones and is in Phase 3 development for the treatment of **C. difficile** associated diarrhea (CDAD), also known as **C. difficile** infection (CDI).
- In the Phase 2 trial for treatment of CDAD, cadazolid clinical cure rates were similar to vancomycin with lower recurrence rates, resulting in higher sustained cure rates (3).
- This study evaluated the activity of cadazolid against recent clinical isolates of **C. difficile** from Europe based on resistance to other antibiotics and prevalent ribotypes.

METHODS

- A total of 652 clinical isolates of **C. difficile** were collected in 2014/2015 from European hospitals.
- The hospitals were located in Belgium (1 site, 20 isolates), Czech Republic (2, 41), France (9, 127), Germany (3, 166), Hungary (1, 29), Poland (1, 20), Romania (3, 59), Spain (5, 115), Sweden (1, 23) and Switzerland (4, 57), with Germany contributing the most isolates (166). A total of 259 isolates were isolated from Europe (2014/2015) from European hospitals.
- Minimum inhibitory concentrations (MICs) for cadazolid and antibiotic comparators were determined by agar dilution following Clinical and Laboratory Standards Institute (CLSI) guidelines (4).
- **C. difficile** isolates were defined as having 'higher' linezolid MICs were those with MIC > 8 mg/L (Table 2).
- Susceptibility was very high to imipenem (92.0%, 600 isolates) and clindamycin (76.4%, 498 isolates) and also high to moxifloxacin at 39.7% (259 isolates). Only 38.5% isolates had 'lower' linezolid MICs (MIC ≤ 8 mg/L).
- Cadazolid MIC distributions were not affected by resistance to other antibiotics (Figures 1-4).
- Overall, 107 different ribotypes were found with the most common (100 isolates, 15.3%). The two next most common ribotypes were ribotype 027 and 078 (Table 3).
- Cadazolid showed consistent activity against other ribotypes with MIC ≤ 0.5 mg/L and MIC ≤ 0.03 mg/L (data not shown).
- The activity of cadazolid was very consistent against other ribotypes with MIC < 0.25 mg/L and MIC < 0.06 mg/L, based on clinical efficacy in treatment of CDAD.
- Cadazolid-resistant isolates (n=498) had a MIC of 1 mg/L.
- Cadazolid-resistant isolates (n=259) had 'higher' linezolid MICs (MIC > 8 mg/L).
- Cadazolid showed consistent activity against European **C. difficile** isolates irrespective of country of origin or ribotype, including the hypervirulent ribotypes 027 and 078.
- Cadazolid activity was not affected by resistance to vancomycin, clindamycin or moxifloxacin; or by raised linezolid MIC.
- The consistent activity of cadazolid against 2014/2015 European isolates supports its continued development for the treatment of CDAD, also known as **C. difficile** infection (CDI).

CONCLUSIONS

We would like to thank the investigators from the ten European countries for providing the isolates for this study.

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