Title: In Vitro Activity of Tebipenem and Comparators against Enterobacterales Collected from Patients with Bloodstream Infections as Part of the Global STEWARD Surveillance Program

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ABSTRACT

Background: Bloodstream infections (BSI) are a significant cause of mortality and morbidity. Enterobacterales (ENT) are frequently implicated in BSI and an increased in organisms producing extended-spectrum-β-lactamase (ESBL). This challenges a potential transition to current oral agents due to co-resistance. Carbapenems are active against ESBL-ENT and tebipenem (TBP) is a new oral carbapenem in clinical development. The aim of the study was to assess resistance (R) among BSI isolates and activity of TBP and carbapenems against ENT collected in a 2019 surveillance study.

Methods: 2019 ENT from BSI were centrally tested by reference broth microdilution. Isolates were from medical centers in the US, Europe (EU), Latin America (LA) and Asia Pacific (AP). MIC results were interpreted according to CLSI, including ESBL assignment. CRE were from medical centers in the US, Europe, Latin America and Asia Pacific.

Results: CRE were from medical centers in the US, Europe, Latin America and Asia Pacific. TBP exhibited similar activity to ertapenem and meropenem against all Enterobacterales from BSI or in combination with other agents due to co-resistance to other classes including the fluorquinolones and trimethoprim-sulfamethoxazole. Among all Enterobacterales resistance rates ≥ 18-20% were observed for the cephalosporins, ESBL, MER-S K. pneumoniae and KPC-2 and -3 were the most prevalent carbapenemases.

Conclusions: TBP is a new oral carbapenem in clinical development that has a similar spectrum of activity to the intravenous carbapenems. The objective of the current study was to assess the prevalence of resistance phenotypes among BSI isolates and the activity of TBP against Enterobacterales collected in the global STEWARD surveillance program during 2019.

INTRODUCTION

Enterobacterales are a predominant cause of bloodstream infections (BSI) with Escherichia coli being the most prevalent pathogen. BSI are a significant cause of morbidity and mortality and are among the most frequently observed hospital-acquired infections (HAIs). The increase in extended-spectrum-β-lactamase (ESBL) producing Enterobacterales further complicates any transition to currently available oral step-down agents due to co-resistance to other classes including the fluorquinolones and trimethoprim-sulfamethoxazole. Although the carbapenems have remained effective against ESBL and AmpC β-lactamase-producing Enterobacterales none are orally bioavailable. Tebipenem (TBP) is an oral carbapenem in clinical development that has a similar spectrum of activity to the intravenous carbapenems. The objective of the current study was to assess the prevalence of resistance phenotypes among BSI isolates and the activity of TBP against Enterobacterales collected in the global STEWARD surveillance program during 2019.

METHODS

A total of 2612 Enterobacterales non-duplicate clinically significant isolates from bloodstream infections were collected from medical centers in 19 countries (Europe 19 countries, Latin America 8 countries), and the United States during 2019. All isolates were shipped to a central laboratory (JMI Laboratories, North Liberty, IA) for identification confirmation. Susceptibility testing was performed using the CLSI broth microdilution reference method and the results were interpreted using CLSI 2020 breakpoints, except in the case of tebipenem where tentative interpretive criteria were used (susceptible ≤0.12 µg/mL, intermediate ≥0.25 µg/mL and resistant ≥0.5 µg/mL). ESBL phenotypes were assigned using CLSI screening criteria for Enterobacterales, Klebsiella pneumoniae, Klebsiella oxytoca and Proteus mirabilis, as these isolates are MIC value ≥2 µg/mL for ceftazidime, ceftriaxone and/or aztreonam. Enterobacterales non-susceptible Enterobacterales were screened for the presence of carbapenemases by whole genome sequencing.

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