INTRODUCTION

- Intravenous (IV) to oral (PO) antibiotic step-down therapy has many benefits, including reducing the length of hospital stay and lowering the risk of nosocomial infections and overall cost [1, 2, 3].
- While fluoroquinolones are utilized as a step-down therapy for the treatment of patients with urinary tract infections, safety concerns [4] and increases in fluoroquinolone-resistant Escherichia coli [5, 6] make this class of agents an increasingly unsuitable option.
- Teipenem is an orally bioavailable carbapenem, which is administered as a pro-drug (teipenem pivoxil/hydrobromide) with broad-spectrum activity against ESBL-positive pathogens, currently in development for the treatment of patients with complicated urinary tract infections (cUTI).

OBJECTIVE

- The objective of these studies was to use 7-day hollow-fiber in vitro infection model assays designed to evaluate the potential of PO teipenem as step-down therapy from IV therapy.

METHODS

Antimicrobial Agent and Challenge Isolates

- A panel of five Escherichia coli isolates were selected based on their known resistance mechanisms and teipenem minimum inhibitory concentration (MIC) values. All isolates were either purchased from ATCC Laboratories (North Liberty, IA) or provided by the National Collection of Type Cultures (NCTC) (Table 1).
- Teipenem was provided by Spero Therapeutics (Cambridge, MA). Ertapenem was purchased from Henry Schein (Melvylk, NY).

Table 1. Known resistance mechanisms and teipenem and ertapenem MIC values of isolates utilized in hollow-fiber in vitro infection model step-down studies

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Known resistance mechanisms</th>
<th>Teipenem MIC (mg/L)</th>
<th>Ertapenem MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli NCTC 13319</td>
<td>CTX-M-15, Sequence Type-12 (S1217)</td>
<td>0.015</td>
<td>0.00</td>
</tr>
<tr>
<td>E. coli ATCC 4643</td>
<td>CTX-M-15, OXA-1 (S13)</td>
<td>0.008</td>
<td>0.015</td>
</tr>
<tr>
<td>E. coli ATCC 1033249</td>
<td>CMY-2, TEM-1, CMY-2/3, TEM-1 (S13, S20)</td>
<td>0.06</td>
<td>0.02</td>
</tr>
<tr>
<td>E. coli ATCC 27822</td>
<td>CTX-M-15, OXA-1, OXA-20 (S13, S20)</td>
<td>0.03</td>
<td>0.015</td>
</tr>
<tr>
<td>E. coli ATCC 13219</td>
<td>CTX-M-15</td>
<td>0.015</td>
<td>0.125</td>
</tr>
</tbody>
</table>

Hollow-Fiber In Vitro Infection Model

- 10 mL of each E. coli isolate were inoculated into the hollow-fiber in vitro infection model cartridges (Rockwell Systems, Frederick, MD) at an inoculum of 1.0 x 10^7 colony forming units (CFU/mL) using Mueller-Hinton broth medium (Figure 1).
- Each hollow-fiber infection model was inoculated with a suspension of 1.0 x 10^7 CFU/mL E. coli ATCC 35218 (University of Michigan, Ann Arbor, MI) as a target challenge isolate.

RESULTS

- Each isolate was challenged in duplicate by an assortment of active and inactive regimens including:
  - IV administration at a 1 g IV dose q24h for 1, 3, 7 days of therapy.
  - Teipenem 600 mg PO q12h was simulated as a step-down therapy, following either 1 or 3 days of ertapenem treatment, as well as a 7-day monotherapy regimen.
  - IV-free control regimens including no treatment, as well as teipenem 1 g IV q12h for 1 or 3 days, followed by a halting of therapy.
- Samples were collected for enumeration of bacterial populations and observation of simulated PK profiles over the duration of the 7-day study period.

Figure 1. Schematic of the hollow-fiber in vitro infection model

Figure 2. As shown in Figure 2, good agreement was observed between the targeted observed concentration-time profiles for teipenem and ertapenem simulated in the hollow-fiber in vitro infection model. An example of the observed concentration-time profiles simulated in the hollow-fiber in vitro infection model for each of the dosing regimens evaluated, are displayed in Figure 4.

Figure 3. Targeted infection concentration time profiles for teipenem and ertapenem in the hollow-fiber in vitro infection model, with observed data overlaid for a sample of evaluated regimens.

Figure 4. Average bacterial burdens observed for five E. coli isolates in the hollow-fiber in vitro infection model evaluated teipenem 1 g IV q12h, and teipenem 600 mg PO q12h dosing regimens as monotherapy and as step-down from IV to PO therapy.

Figure 5. Targeted concentrations and IC50 values for teipenem and ertapenem in hollow-fiber in vitro infection model.

Figure 6. Targeted concentrations and IC50 values for teipenem and ertapenem in hollow-fiber in vitro infection model.

CONCLUSIONS

- These data demonstrate the potential utility of teipenem as an PO step-down from IV therapy for the treatment of cUTI arising from E. coli, including those producing ESBL. These data also suggest the need to evaluate teipenem as a PO step-down after administration of other IV therapies.

REFERENCES

- 2. Savic J, Cotroneo N, Ambrose PG. Retreatment of teipenem 600 mg PO q12h dosing regimens successfully reduced the bacterial burden to densities lower than that of the initial burden, as well as lower limit of detection, for all five isolates evaluated over the 7-day period.