Herein, we describe a series of 10-day hollow-fiber infection model (HFIM) studies. ME1100 (arbekacin inhalation solution) is in clinical development for the treatment of ventilator-associated bacterial pneumonia (VABP) and hospital-acquired bacterial pneumonia (HAP), and in the treatment of extended-spectrum beta-lactamases and P. aeruginosa. The HFIM has been previously utilized to determine antibiotic exposures required to prevent the emergence of drug-resistant subpopulations in the model. In brief, this pharmacodynamic system mimics the pharmacokinetic (PK) exposure of arbekacin.

METHODS

Arbekacin was provided by Meiji Seika Pharma Co. Ltd. (Tokyo, Japan). The PK profile of ME1100-observed in patient and healthy volunteers (N=12), after inhalation via a face-mesh nebulizer, was generated using data obtained from a Phase 1b study supplied by the Meiji Seika Pharma Co. Ltd.

The four clinical isolates utilized in the HFIM studies. S. aureus ATCC 33591 was purchased from the American Type Culture Collection (ATCC, Manassas, VA), and S. aureus 2847 and P. aeruginosa 12623 from HM Laboratories (North Liberty, IA). P. aeruginosa H2056 was provided by Meiji Seika Pharma Co. Ltd.

Hollow-Fiber Infection Model

The HFIM was developed to determine antibiotic exposures required for prevention of drug-resistant subpopulations in the model. The HFIM is a semi-artificial, two-compartment system, which is separated from a central compartment by semi-permeable membranes. The central compartment contains half-life-targeting PK profiles of arbekacin. The peripheral compartment contains 1 mL samples were collected for drug concentration assay over the first 48 hours and 1 mL samples were obtained over the study duration, washed twice with sterile saline, and serially diluted, and quantitatively cultured as follows:

- In vitro activity against S. aureus ATCC 33591 and P. aeruginosa H2056 was assessed.
- Microbroth and agar-dilution MIC values of isolates utilized in the HFIM studies were obtained from the American Type Culture Collection (ATCC, Manassas, VA) and the Clinical and Laboratory Standards Institute [1].

RESULTS

To utilize the HFIM to determine the arbekacin exposure, required to prevent the emergence of drug-resistant subpopulations from a panel of S. aureus and P. aeruginosa clinical isolates over a 10-day study duration.

These data provided a dose selection approach for ME1100 in the treatment of patients with HABP/VABP.


drug-resistant subpopulations isolated from the HFIM over a 48-hour period (B) and an example of an arbekacin exposure simulated in the HFIM (A).

<table>
<thead>
<tr>
<th>Challenge Isolate</th>
<th>Arbekacin MIC values of S. aureus from the HFIM</th>
<th>Arbekacin MIC values of P. aeruginosa from the HFIM</th>
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</thead>
<tbody>
<tr>
<td>S. aureus ATCC 33591</td>
<td>1 - 256</td>
<td>1 - 256</td>
</tr>
<tr>
<td>P. aeruginosa H2056</td>
<td>1 - 256</td>
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</tr>
</tbody>
</table>

Figure 3. Relationships between change in log_{10} CFU/mL from baseline and arbekacin total-drug ELF AUC:MIC ratios on Day 10 for S. aureus and P. aeruginosa. These data suggest that when arbekacin exposure thresholds are achieved in a clinical setting, on-therapy resistance can be minimized.

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