INTRODUCTION & PURPOSE

Background: Lefamulin is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans. Pleuromutilins specifically inhibit bacterial protein synthesis by binding to the A- and P-site of the peptidyl transferase center ('induced fit'). Lefamulin displays potent in vitro activity against a variety of pathogens that cause skin and soft tissue infections, respiratory tract infections including Gram-positive, fastidious Gram-negative, and atypical bacteria including Mycoplasma pneumoniae, Chlamydia pneumophila pneumoniae and Legionella pneumophila.

Lefamulin was shown to be highly active in the lung in vivo and to be unaffected by the presence of surfactant. Furthermore, it has been well tolerated in phase 1 and 2 trials. Lefamulin is currently in Phase 3 trials for the treatment of community-acquired bacterial pneumonia (CAP) in adults.

S. aureus is a well-recognized cause of pneumonia from both the community and hospital setting. The clinical management of staphylococcal pneumonia is complicated by the high prevalence of methicillin-resistance observed in S. aureus (MRSA) and the invasive infection it causes. This study investigated the susceptibility of S. aureus strains collected from patients hospitalized with pneumonia in Europe in 2015 to lefamulin and comparators commonly used to treat CAP.

METHODS

510 unique S. aureus isolates were collected from hospitalized patients with pneumonia in 19 European countries including Belarus, Belgium, Czech Republic, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Poland, Portugal, Romania, Russia, Slovenia, Spain, Sweden, Turkey and United Kingdom (33 sites) in 2015 as part of the SENTRY surveillance program. Only one isolate per patient infection episode was included in surveillance.

Lefamulin and comparators were tested by CLSI broth microdilution methods and susceptibility was determined using the EUCAST (2017) breakpoints. QC reference organisms were tested concurrently for lefamulin and comparator agents.

RESULTS

- Lefamulin was the most potent compound tested, with 99.8% of all isolates being inhibited at a concentration of ≤0.25 mg/L and MIC90/90 values of 0.06/0.06 mg/L (Table 1).

Table 1. In vitro activity of lefamulin and comparators against S. aureus.

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC90 (mg/L)</th>
<th>MIC90 (mg/L)</th>
<th>% Susceptible*</th>
<th>% Resistance†</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus, total (510)</td>
<td>0.06</td>
<td>0.12</td>
<td>21.8</td>
<td>78.2</td>
</tr>
<tr>
<td>S. aureus, MSSA (170)</td>
<td>0.06</td>
<td>0.12</td>
<td>24.3</td>
<td>75.7</td>
</tr>
<tr>
<td>S. aureus, MRSA (440)</td>
<td>0.06</td>
<td>0.12</td>
<td>72.9</td>
<td>27.1</td>
</tr>
</tbody>
</table>

- Overall, susceptibility rates were >90% for clindamycin (MIC90/90, ≤0.25 mg/L), daptomycin (MIC90/90, 0.5 mg/L), doxycycline (MIC90/90, 0.06 mg/L), vancomycin (MIC90/90, 0.5/1 mg/L), linezolid (MIC90/90, 1 mg/L) and cefaroline (MIC90/90, 0.25/1 mg/L). 21% of isolates (n=307) were oxacillin-resistant (MRSA).

- All MRSA were inhibited by lefamulin (MIC range, 0.03-0.25 mg/L; MIC90/90, 0.06/0.32 mg/L), MRSA were fully susceptible (100%) to vancomycin and daptomycin and ≥99% of MRSA were susceptible to linezolid.

- MRSA strains showed limited susceptibility to azithromycin (72.9% resistant), levofloxacin (88.8% resistant), clindamycin (30.8% resistant) and cefaroline (24.3% resistant).

- 71 isolates (66.4%) were resistant to at least three antibiotic classes (macrolides, fluoroquinolones and oxacillin), all of which were inhibited by a lefamulin concentration of ≤0.5 mg/L.

- Resistance rates among MSSA were generally lower than among MRSA.

- Azithromycin displayed the highest resistance rates of 20.1%.

CONCLUSIONS

- S. aureus strains collected from patients hospitalized with pneumonia were highly susceptible to lefamulin regardless of susceptibility phenotype to the other antibiotics tested.

- Lefamulin was highly active against multi-drug resistant (MDR) S. aureus.

- Due to its potent activity against MDR-resistant S. aureus, the most prevalent typical and atypical respiratory pathogens, and the availability of IV and oral formulations, lefamulin has the potential to play a role in the empiric treatment of CAP.

REFERENCES

(3) Paukner, et al. AAC 57(9), 4489-4495 (2013)
(7) CLSI, M31-A9(2017)
(8) EUCAST. Breakpoint tables for interpretation of MICs and zone diameters V. 7.0 (2017)