RESULTS cont.

MISA (grown at 37°C in MHB for 16 h) suspension in saline was used for intraperitoneal infection of NMRI mice (n=8).

The challenge dose was approximately 2 x 10^7 CU per mouse, which randomized for the immune deficient infection model were given cyclophosphamide (Endoxan, Baxter, Germany) intraperitoneally twice prior to bacterial challenge. The first dose of 150 mg/kg was given four days before the challenge and the second dose of 100 mg/kg was given one day before the challenge. This pre-treatment regimen resulted in a reliable, transient leucopenia and neutropenia in mice that lasted for three days after the last dose of cyclophosphamide was given.

The antibacterial subcutaneous (SC) challenge was initiated one hour after infection as a single dose. The single dose of lefamulin (70 mg/kg), daptomycin (22.5 mg/kg), vancomycin (160 mg/kg), linezolid (80 mg/kg) and tigecycline (6.5 mg/kg) were selected to mimic respective therapeutic human exposures.

Prior to treatment (Early Control) and at 24 h after start of therapy designated groups of animals were euthanized for blood titer determination. None of the untreated control animals survived beyond 24 h post challenge. Dead animals were included into the analysis with a log_{10} CFU/mL of 7.3. The lower limit of quantification was 1.3 log_{10} CFU/mL. For statistics all values below LLOQ (1.3 log_{10} CFU/mL) were handled as LLOQ/2.

A one way ANOVA was used for statistical analysis (SigmaStat, 3.11). The efficacy of lefamulin compared to the reference compounds was analyzed by Bonferroni’s multiple-comparison procedure. P < 0.05 was considered as statistically significant.

Data were depicted as column plots and box plots using the software package Graphpad Prism 6.1.

METHODS

Lefamulin treatment led to a significant decrease in CFU/mL within 24 h very irrespective of the immune status (Figure 1).

This study supports continued evaluation of lefamulin for as a potential treatment of staphylococcal bacteremia.

RESULTS

• In the non-neutropenic murine model the efficacy of all tested antibiotics showed a statistically significant decrease of CFU/mL compared to the initial bacterial burden in the blood (Early Control; EC) (Figure 18).

• In the immune deficient animal model only linezolid showed no significant difference in CFU/mL compared to the EC (Figure 14).

• Irrespective of the immuno status, the reduction in blood titers caused by lefamulin was >4 log_{10} CFU/mL and significantly greater than those observed for daptomycin, vancomycin and linezolid, respectively (Figure 14).

• Lefamulin treatment led to a significant decrease in CFU/mL within 24 h similar to that of the bactericidal drugs daptomycin and vancomycin, both recommended for the treatment of bacteremia caused by S. aureus, (Table 1).

• Lefamulin showed in vivo bactericidal properties comparable to daptomycin, irrespective of the immune status (Figure 1).

REFERENCES


Table 1: Efficacy of lefamulin and reference antibiotics against S. aureus (893; MSSA; ATCC 700695) in the murine bacteremia model

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose [mg/kg/day]</th>
<th>MIC [µg/mL]</th>
<th>Bactericidal Index (CI)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Control</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lefamulin</td>
<td>0.06</td>
<td>32</td>
<td>1.98 ± 0.68</td>
<td>a</td>
</tr>
<tr>
<td>Linezolid</td>
<td>0.25</td>
<td>16</td>
<td>1.9 ± 1.06 ± 0.02</td>
<td>b</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>80</td>
<td>1</td>
<td>15</td>
<td>5.75 ± 1.34*</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>22.5</td>
<td>0.25</td>
<td>16</td>
<td>1.86 ± 1.02</td>
</tr>
</tbody>
</table>

*P < 0.05 compared with Early Control (Dunnett´s method).

CONCLUSIONS

• Lefamulin showed therapeutic outcome comparable to DAP or VAN in this acute experimental infection model, while showing superior killing as compared to LZD or TGC.

• The efficacy of lefamulin was maintained under neutropenic conditions with >4log_{10} CFU/mL at clinically relevant exposures.

• This study supports continued evaluation of lefamulin for as a potential treatment of staphylococcal bacteremia.