Correspondence


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Activity of iclaprim against Legionella pneumophila

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Sir,

Legionella pneumophila is an ‘atypical’ pathogen associated with lower respiratory tract infections (RTIs) such as community-acquired pneumonia (CAP). Organizations such as the Infectious Diseases Society of America recommend that empirical treatment of CAP should cover atypical pathogens such as L. pneumophila and Chlamydia pneumoniae. At present, macrolides and fluoroquinolones are the most active options against atypical pathogens. On the contrary, β-lactams are inactive against these pathogens.

Iclaprim is a new dihydrofolate reductase inhibitor, which recently completed enrolment in two Phase III trials of complicated skin and skin structure infections treated via intravenous administration and has recently successfully completed Phase I investigations of an oral formulation. Currently, the only clinically available antibiotic targeting dihydrofolate reductase is trimethoprim. This antibiotic can be used in combination with sulphonamides such as sulfamethoxazole, although rarely these drugs due to concerns over toxicity with sulfamethoxazole. At present, data on the activity of iclaprim against L. pneumophila have not been published.

Iclaprim (Arpida AG, Reinach, Switzerland), trimethoprim, sulfamethoxazole, trimethoprim/sulfamethoxazole (19:1 ratio), clarithromycin and levofloxacin (all from Sigma, Poole, UK) were investigated against 56 L. pneumophila isolates. The isolates were derived mostly from clinical material examined in hospitals or reference centres worldwide. MICs were determined using an agar dilution method. The agar consisted of 1% yeast extract (Oxoid Ltd, Basingstoke, UK), 1.3% Bacteriological Agar No. 1 (Oxoid), 5% water-lysed horse blood (Oxoid) and legionella growth supplement (Oxoid). The inoculum used was ~105 cfu of each isolate contained in a volume of 1 μL. After 48–72 h of incubation in air at 35°C, MIC was determined as the lowest concentration of antimicrobial tested that inhibited growth of the inoculum, disregarding a single persisting colony or a faint haze caused by inoculation.

Summary MIC data are presented in Table 1. Iclaprim was very active, with 16-fold lower MIC50 or MIC90 values than...
Table 1. Activity of iclaprim and comparators against Legionella pneumophila

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>50%</th>
<th>90%</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iclaprim</td>
<td>0.03</td>
<td>0.06</td>
<td>0.008–0.12</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>0.5</td>
<td>1</td>
<td>0.25–2</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>64</td>
<td>128</td>
<td>16–256</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>0.12</td>
<td>0.25</td>
<td>0.12–0.25</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.03</td>
<td>0.03</td>
<td>0.008–0.03</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0.008</td>
<td>0.008</td>
<td>0.004–0.015</td>
</tr>
</tbody>
</table>

trimethoprim alone. Sulfamethoxazole was essentially inactive and the combination of trimethoprim and sulfamethoxazole was also less active than iclaprim, despite showing a 4-fold synergy when compared with trimethoprim alone. Iclaprim had activity similar to that observed with clarithromycin, but was less active than levofloxacin.

These data show that iclaprim has promising in vitro activity against L. pneumophila. These results, in combination with its high concentration in alveolar macrophages and epithelial lining fluid,3 oral bioavailability and activity against other RTI pathogens such as Streptococcus pneumoniae, Haemophilus influenzae, Streptococcus pyogenes4 and C. pneumoniae,5 make iclaprim a potentially useful new agent for the treatment of RTIs.

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Transparency declarations

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References