Activity of iclaprim against clinical isolates of Streptococcus pyogenes and Streptococcus agalactiae

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Sir,

β-Haemolytic streptococci, especially Streptococcus pyogenes and Streptococcus agalactiae, are frequently responsible for a diverse range of clinical manifestations, from mild skin/soft tissue infections and pharyngitis to more serious diseases, such as bacteraemia, cellulitis, puerperal sepsis, meningitis, pneumonia and necrotizing fasciitis.1,2 Isolates of S. pyogenes are universally susceptible to penicillin and consequently few laboratories routinely perform susceptibility testing with this organism. In Europe, the prevalence of macrolide resistance among S. pyogenes rose from 10.4% in 2002–03 to 11.6% in 2004–05.3 Similarly, in the USA, the Centers for Disease Control and Prevention provided national surveillance data that reported a gradual trend of increasing macrolide resistance of S. pyogenes from 4% to 5% in 1996–98 to 8% to 9% in 1999–2001 while 99.5% of isolates remained susceptible to clindamycin.4 Like S. pyogenes, S. agalactiae remains fully susceptible to penicillin. However, erythromycin and erythromycin/clindamycin resistance of S. agalactiae have been reported to be 22% and 6%, respectively.5

Iclaprim is a novel diaminopyrimidine inhibitor within the same class as trimethoprim but with more potent and bacterial in vitro activity against major Gram-positive pathogens in complicated skin and soft tissue infections (cSSTIs), including Staphylococcus aureus, S. pyogenes and S. agalactiae.6 An intravenous formulation of iclaprim has completed Phase III trials for cSSTIs. In addition, Phase II trials of iclaprim administered by intravenous infusion for patients with hospital-acquired and ventilator-associated pneumonia and of an oral formulation of iclaprim as step-down therapy for patients with cSSTIs are ongoing.6 Considering the importance of such streptococci in the aetiology of cSSTIs and the emergence of resistance to several clinically used antibiotics, the current study was designed to investigate the in vitro activity of iclaprim and comparators against S. pyogenes and S. agalactiae, the key causative pathogens in cSSTIs.

The in vitro activities of iclaprim (Arpida AG, Reinach, Switzerland), trimethoprim/sulfamethoxazole (1:19 ratio), clarithromycin, clindamycin, linezolid, penicillin G, levofloxacin and vancomycin were investigated against 500 S. pyogenes and 44 S. agalactiae. Isolates tested were non-repeat isolates collected during 2006–07 from clinical material including respiratory and wound infections from hospitals in 10 European countries. MIC determinations were carried out using CLSI broth microdilution methodology with cation-adjusted Mueller–Hinton broth supplemented with 5% (v/v) lysed horse blood.7

Summary MIC data are presented in Table 1. Iclaprim exhibited potent activity against all S. pyogenes isolates. When comparing the MIC90 of iclaprim and comparators, iclaprim (MIC90 0.06 mg/L) was 16 times more active than co-trimoxazole (MIC90 1 mg/L) and levofloxacin (MIC90 1 mg/L), 32 times more active than linezolid (MIC90 2 mg/L) and 8 times more active than penicillin (MIC90 0.06 mg/L). Such activity may aid in replacing penicillin where resistance is increasing.8 When comparing the MIC90 of S. pyogenes and S. agalactiae, linezolid and penicillin were the agents with the broadest activity.

Table 1. Activity of iclaprim and comparators against S. pyogenes and S. agalactiae

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>S. pyogenes (n = 500)</th>
<th>S. agalactiae (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC90 (mg/L)</td>
<td>range (mg/L)</td>
</tr>
<tr>
<td>Iclaprim</td>
<td>0.06</td>
<td>0.015–0.25</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>1</td>
<td>0.03–2</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.06</td>
<td>≤0.015 to ≥64</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.06</td>
<td>≤0.015 to ≥64</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>1</td>
<td>0.25–4</td>
</tr>
<tr>
<td>Linezolid</td>
<td>2</td>
<td>0.5–2</td>
</tr>
<tr>
<td>Penicillin</td>
<td>0.015</td>
<td>0.004–0.03</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.5</td>
<td>0.25–1</td>
</tr>
</tbody>
</table>
than vancomycin (MIC<sub>90</sub> 0.5 mg/L). Penicillin was the only compound that was more active than iclaprim with a 2-fold lower MIC<sub>90</sub>. Importantly, iclaprim exhibited potent activity against the subset of 45 macrolide-resistant isolates with an MIC<sub>90</sub> of 0.03 mg/L (data not shown) and the subset of 20 macrolide-resistant/clindamycin-resistant isolates (MIC<sub>90</sub> 0.03 mg/L, data not shown).

Furthermore, iclaprim was active against all S. agalactiae isolates with an MIC<sub>90</sub> of 0.25 mg/L, which was comparable to those of co-trimoxazole (MIC<sub>90</sub> 0.5 mg/L), penicillin (MIC<sub>90</sub> 0.12 mg/L) and vancomycin (MIC<sub>90</sub> 0.5 mg/L). Moreover, against this species, iclaprim was 4 times more active than levofloxacin, 8 times more potent than linezolid and clarithromycin and at least 256 times more active than clindamycin. Of the 44 isolates tested, 6 were macrolide-resistant, for which iclaprim exhibited an MIC range of 0.06–0.5 mg/L (data not shown). Of these, one isolate was macrolide- and clindamycin-resistant, for which iclaprim exhibited an MIC of 0.06 mg/L (data not shown).

Trimethoprim and its 1:19 combination with sulfamethoxazole, co-trimoxazole, have been used extensively in clinical practice for more than 40 years. Although co-trimoxazole is often used for the treatment of cSSTsIs, it is often considered ineffective for infections due to S. pyogenes. In contrast, in two Phase III clinical trials of cSSTsIs, iclaprim exhibited good eradication rates for S. pyogenes. Considering the importance of β-haemolytic streptococcal species in the aetiology of cSSTsIs and the emergence of resistance to several clinically used antibiotics, these data further demonstrate the potential for iclaprim to treat infections caused by S. pyogenes and S. agalactiae in cSSTsIs.

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Daptomycin for the treatment of vancomycin-resistant enterococcal infections

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Sir,

Vancomycin-resistant enterococci (VRE) are an important cause of nosocomial bloodstream infection (BSI) due to increased mortality compared with vancomycin-susceptible strains and limited...