Antimicrobial Vancomycin 0.5 0.25–1 0.5 0.5–1
Penicillin 0.015 0.004–0.03 0.12 0.06–0.12
Linezolid 2 0.5–2 2 1–2
Levofloxacin 1 0.25–4 1 0.5–2
Clindamycin 0.06

versally susceptible to penicillin and consequently few
organisms. In Europe, the prevalence of macrolide resistance
among S. pyogenes rose from 10.4% in 2002–03 to 11.6% in
2004–05. 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 clindamy-
cin. Like S. pyogenes, S. agalactiae remains fully susceptible to
penicillin. However, erythromycin and erythromycin/clindamy-
cin resistance of S. agalactiae have been reported to be 22% and
6%, respectively.

Iclaprim is a novel diaminopyrimidine inhibitor within the
same class as trimethoprim but with more potent and bacteri-
cidal in vitro activity against major Gram-positive pathogens in
complicated skin and soft tissue infections (cSSTIs), including
Staphylococcus aureus, S. pyogenes and S. agalactiae. An intrave-
nous 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. 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 com-
parators 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), clari-
thromycin, 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 sup-
plemented with 5% (v/v) lysed horse blood.

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

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 ≥0.64</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.06</td>
<td>≤0.015 to ≥0.64</td>
</tr>
<tr>
<td>Levofloxacin</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\textsubscript{90} 0.5 mg/L). Penicillin was the only compound that was more active than iclaprim with a 2-fold lower MIC\textsubscript{90}. Importantly, iclaprim exhibited potent activity against the subset of 45 macrolide-resistant isolates with an MIC\textsubscript{90} of 0.03 mg/L (data not shown) and the subset of 20 macrolide-resistant/clindamycin-resistant isolates (MIC\textsubscript{90} 0.03 mg/L, data not shown).

Furthermore, iclaprim was active against all S. agalactiae isolates with an MIC\textsubscript{90} of 0.25 mg/L, which was comparable to those of co-trimoxazole (MIC\textsubscript{90} 0.5 mg/L), penicillin (MIC\textsubscript{90} 0.12 mg/L) and vancomycin (MIC\textsubscript{90} 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 cSSSTIs, it is often considered ineffective for infections due to S. pyogenes. In contrast, in two Phase III clinical trials of cSSSTIs, iclaprim exhibited good eradication rates for S. pyogenes. Considering the importance of β-haemolytic streptococcal species in the aetiology of cSSTIs 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 cSSSTIs.

Acknowledgements

Preliminary data were presented at the Eighteenth European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Barcelona, Spain, 2008 (Abstract O100).

Funding

This study was sponsored by Arpida AG.

Transparency declarations

I. M. has received funds from numerous pharmaceutical companies for research and consultancy on antimicrobial compounds. S. H. was employed by Arpida AG. K. M. has nothing to declare.

References