Antimicrobial activity of iclaprim tested against recent \textit{S. aureus} clinical isolates: Results from the International Study of Iclaprim Susceptibility (ISIS).

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ABSTRACT

Background: Iclaprim (ICL) is a novel dihydrofolate reductase inhibitor with broad antibacterial activity. We evaluated the comparative potency and bactericidal activity (MBC) of ICL tested against a large collection of clinical \textit{Staphylococcus aureus} strains.

Methods: 4,516 clinical isolates (2,517 from the USA and 2,057 from Europe) selected in 2002-2004 were susceptible (S) tested by CLSI broth microdilution method against ICL, trimethoprim (TMP), co-trimoxazole (TMP/SMX) and various comparators. MBC values for ICL, TMP and VAN were assessed for a subset of 46 strains.

Results: ICL was generally 16-fold more potent than TMP and VAN and was equally potent at TMP/SMX (Table). 95\% of strains were inhibited at $0.12\ \mu g/mL$ for ICL. ICL was equally active against meningitis S (MSSA) and MRSA isolates from the USA ($MBC_{50}$ $0.12\ \mu g/mL$ for both). In EU, MRSA showed ICL MIC values slightly higher than MSSA ($MBC_{50}$ $1\ \mu g/mL$ for both). ICL showed superior bactericidal activity to VAN. ICL MBC/MIC ratios for MRSA isolates from the USA were assessed for a subset of 41 strains.

Conclusions: ICL was very active and highly bactericidal against recent clinical S. aureus strains and its activity was not adversely affected by resistance to clindamycin or other antimicrobials tested. ICL showed superior bactericidal activity than VAN against MRSA.

INTRODUCTION

Iclaprim is a novel investigational drug, which is being developed for various Gram-positive bacterial infections. The compound has been granted fast-track status by the US Food and Drug Administration for infection caused by \textit{Staphylococcus aureus}. ICL has a unique mechanism of action: It inhibits dihydrofolate reductase, thereby enhancing the potency and bactericidal activity as well as reducing the potential for resistance development. This study provides useful information to help optimize the use of ICL in clinical practice.

METHODS

Background: Iclaprim (ICL) is a novel dihydrofolate reductase inhibitor (DHFR) belonging to the diaminopyrimidine class of antibacterial agents. It inhibits DHFR and thus inhibits the synthesis of folates. DHFR is essential for bacterial growth. ICL has a unique mechanism of action: It inhibits dihydrofolate reductase, thereby enhancing the potency and bactericidal activity as well as reducing the potential for resistance development. In the present study, we evaluated the comparative potency and bactericidal activity of iclaprim tested against a large collection of clinical \textit{S. aureus} strains.

RESULTS

Iclaprim was very active against \textit{S. aureus} ($MIC_{90} 0.06\ \mu g/mL$ and $MBC_{90} 0.12\ \mu g/mL$) (Table 1), with over 95\% of the strains being inhibited at $0.12\ \mu g/mL$. Iclaprim was 16-fold more potent than TMP ($MIC_{50} 1\ \mu g/mL$), MBC ($MBC_{50} 2\ \mu g/mL$). ICL showed bactericidal activity against the vast majority of \textit{S. aureus} clinical isolates tested. ICL showed superior activity against MRSA isolates from the USA than against isolates from Europe (Table 2).

Conclusions: ICL was very active and highly bactericidal against recent clinical \textit{S. aureus} strains and its activity was not adversely affected by resistance to clindamycin or other antimicrobials tested. ICL showed superior bactericidal activity than VAN against MRSA.

REFERENCES


\textsuperscript{1} Iclaprim exhibited bactericidal activity against the vast majority of \textit{Staphylococcus} clinical isolates tested. With \textit{MIC} values of $0.06\ \mu g/mL$, against MRSA in vitro. 12 of the 21 MRSA isolates tested (Table 2).

\textsuperscript{2} Iclaprim exhibited similar activities against \textit{S. aureus} ($MIC_{90} 0.06\ \mu g/mL$) and against \textit{S. pneumoniae} ($MIC_{90} 0.015–8\ \mu g/mL$) and showed in-vitro activity similar to that of the TMP/SMX combination, but activity was somewhat lower against MRSA isolates from the USA than against isolates from Europe (Table 1).

\textsuperscript{3} The activity of iclaprim against MSSA ($MIC_{90} 0.06\ \mu g/mL$ and $MIC_{90} 0.12\ \mu g/mL$) for both strains. ICL showed superior bactericidal activity to VAN. ICL MBC/MIC ratios for MRSA isolates from the USA were assessed for a subset of 41 strains.

\textsuperscript{4} Iclaprim was very active against \textit{S. aureus} ($MIC_{90} 0.06\ \mu g/mL$ and $MIC_{90} 0.12\ \mu g/mL$) (Table 1), with over 95\% of the strains being inhibited at $0.12\ \mu g/mL$. Iclaprim was 16-fold more potent than TMP ($MIC_{50} 1\ \mu g/mL$), MBC ($MBC_{50} 2\ \mu g/mL$). ICL showed bactericidal activity against the vast majority of \textit{S. aureus} clinical isolates tested. ICL showed superior bactericidal activity than VAN against MRSA.

\textsuperscript{5} The activity of iclaprim against MSSA ($MIC_{90} 0.06\ \mu g/mL$ and $MIC_{90} 0.12\ \mu g/mL$) for both strains. ICL showed superior bactericidal activity to VAN. ICL MBC/MIC ratios for MRSA isolates from the USA were assessed for a subset of 41 strains.

\textsuperscript{6} Iclaprim exhibited bactericidal activity against the vast majority of \textit{Staphylococcus} clinical isolates tested. With \textit{MIC} values of $0.06\ \mu g/mL$, against MRSA in vitro. 12 of the 21 MRSA isolates tested (Table 2).

Table 1. Activity of comparator agents tested against \textit{S. aureus} from the USA and Europe.

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<tr>
<th>Antimicrobial agent (no. tested)</th>
<th>$MIC_{90}$</th>
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