Bactericidal activity and post antibiotic effect of iclaprim (ICL) against Staphylococcus aureus (SA)

M. E. Jones, D. C. Draghi, P. K. Grover, S. Hawser, K. Islam and D. F. Sahm

Eurorhin Medical Anti-Infective Services, Hemelton, Virginia, USA; Arpida AG, Riehen, Switzerland

ABSTRACT

Background: Iclaprim is in Phase III clinical development for the treatment of serious skin infections caused by penicillin-resistant pathogens. Previous reports have shown that ICL is active against methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-intermediate and vancomycin-resistant S. aureus (VISA, VRSA), Staphylococcus epidermidis, and enterococcal pathogens. The aim of this study was to determine the bactericidal activity (BA) and the post-antibiotic effect (PAE) of ICL against Staphylococcus aureus.

Methods: BA was evaluated against methicillin-resistant S. aureus (ATCC 33225), vancomycin-intermediate S. aureus (ATCC 25923), vancomycin-resistant S. aureus (ATCC 33222), Staphylococcus epidermidis, and enterococcal pathogens. The MIC of each strain was determined by the broth microdilution method and is reported in Table 1. Results of BA were determined by exposing bacterial isolates to ICL and comparing the number of colony forming units (CFUs) at each time point against ICL at concentrations of 1, 5, and 10X MIC for 1 hour (5X MIC for S. epidermidis and enterococci). BA for ICL resulted in more rapid killing when compared with comparators (Figure 1). CONCLUSIONS: ICL is very active against all S. aureus isolates, irrespective of their resistance phenotype/genotype with MICs ranging between 0.25 and 1.0 μg/mL. Together these data support the clinical utility of ICL in various infections caused by MRSA.

BACKGROUND

Iclaprim is a novel diaminopyrimidine that irreversibly inhibits dihydrofolate reductase (DHFR), the target enzyme of Trimethoprim (TMP). ICL is in Phase III clinical development for the treatment of serious skin infections caused by penicillin-resistant pathogens. Previous reports have shown that ICL exhibited rapid BA and a PAE against clinical isolates of MRSA including VAN- and LZD-resistant strains.

METHODS

Clinical isolates from worldwide sources were selected from the Europhus collection and isolates were contributed from the Centers for Disease Control and Prevention (CDC) and the Hospital Infections Program (HIP). Resistance in S. aureus respiratory isolates was determined by broth microdilution and MIC was interpreted using CLSI criteria. Results of BA were determined by exposing bacterial isolates to ICL and comparing the number of colony forming units (CFUs) at each time point against ICL at concentrations of 1, 5, and 10X MIC for 1 hour (5X MIC for S. epidermidis and enterococci). BA for ICL resulted in more rapid killing when compared with comparators (Figure 1).

RESULTS

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ICL exhibited rapid BA and a PAE against the strains in this study. As a representative strain, SA 1343142, 2X MIC was defined as a 1-log reduction in CFUs, and NT=Not tested; CLSI interpretation for that agent was resistant and was not tested.

CONCLUSIONS

Iclaprim exhibited rapid bactericidal activity against the strains in this study, which represent several diverse groups of S. aureus that predominates in serious infections, including resistant strains. Antibacterial and bactericidal activities were not affected by the resistance phenotype/ genotype or MIC and MBC in susceptible strains, and were generally similar to those of the comparator agents (Table 2).

REFERENCES