Surveillance of iclaprim activity: *in vitro* susceptibility of *Staphylococcus aureus* resistant to clindamycin/tetracycline and beta-haemolytic streptococci resistant to macrolides/tetracyclines among skin and skin-structure pathogens collected during 2015-2016 from Europe and North America

David B Huang, MD, PhD,[1*] Nadia Tocci,[2] Sophie Magnet, PhD,[2] Stephen Hawser, PhD[2]

[1]Motif BioSciences, Princeton, New Jersey, Rutgers New Jersey Medical School, Trenton, New Jersey, USA, [2]IHMA Europe Sàrl, Route de l'Ile-au-Bois 1A, 1870 Monthey (VS) Switzerland

Abstract

Background: Iclaprim is a diaminopyrimidine, which inhibits bacterial dihydrofolate reductase. In an era of increasing antimicrobial resistance, iclaprim and comparators antibiotics were tested against skin and skin structure pathogens collected during 2015-2016 from Europe and North America, including isolates of *S. aureus* resistant to clindamycin/tetracycline and beta-haemolytic streptococci resistant to macrolides/tetracycline.

Methods: 618 Isolates of *S. aureus* and 313 beta-hemolytic streptococci underwent antibacterial susceptibility testing at IHMA. Susceptibility testing was performed by broth microdilution in accordance with the Clinical and Laboratory and Standards Institute (CLSI) guidelines. Minimum inhibitory concentration (MIC) interpretations were based on CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria.

Results: Iclaprim MIC_{50}/MIC_{90} for *S. aureus* resistant to clindamycin/tetracycline and beta-haemolytic streptococci resistant to macrolides/tetracyclines are shown in Table 1.

Conclusion: Iclaprim is active against select *S. aureus* resistant to clindamycin/tetracycline and beta-haemolytic streptococci resistant to macrolides/tetracyclines from skin and skin structure pathogens collected during 2015-2016 from Europe and North America.

Background

Iclaprim is a novel diaminopyrimidine, which inhibits bacterial dihydrofolate reductase, a critical enzyme in the bacterial folate synthesis pathway. Iclaprim is active against MRSA resistant or nonsusceptible to vancomycin, linezolid and daptomycin [1].In two Phase 3 clinical trials, iclaprim has shown clinical response comparable to vancomycin among patients treated for skin and skin structure infections [2,3].The objective of this study was to determine the activity of iclaprim against *S. aureus* isolates resistant to clindamycin/tetracycline and beta-haemolytic streptococci resistant to macrolides/tetracycline.

Methods

Clinical isolates

Clinical isolates (464 from Europe and 467 from North America) were identified by submitting laboratories and confirmed by IHMA Laboratories using the Bruker Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOP) biotyper for all isolates.

MIC Determination and Interpretation

MIC tests were performed by broth microdilution in line with CLSI susceptibility testing standards [4]. MIC interpretations were based on CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria [4,5].

Results

Iclaprim and comparator antibiotic MIC results were within the CLSI published ranges against *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619. Iclaprim MIC_{50}/MIC_{90} and cumulative MIC distribution (%) for *S. aureus* resistant to clindamycin/tetracycline and beta-haemolytic streptococci resistant to macrolides/tetracycline are shown in Table 1. Figures 1, 2 and 3, show cumulative percent MIC distributions for iclaprim against *S. aureus*, MRSA/MSSA and beta-haemolytic streptococci, respectively.

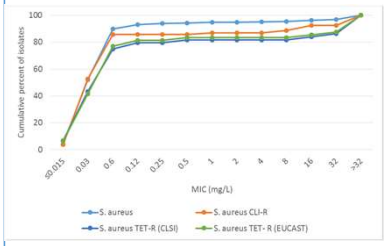
Iclaprim was active against the majority of isolates and had low MIC_{50} for all phenotypes ranging from 0.03 – 0.06 mg/L. MIC_{90} for all *S. aureus* (n = 618) was 0.12 mg/L though MIC_{90}'s were higher for a number of sub-group phenotypes. MIC_{90} for streptococci were only slightly changed with respect to different phenoytpes.

Table 1: Iclaprim MIC_{50}/MIC_{90} for *S. aureus* resistant to clindamycin/tetracycline and beta-haemolytic streptococci resistant to macrolides/tetracyclines

Phenotype	n	MIC_{50}	MIC_{90}
S. aureus	618	0.03	0.12
S. aureus CLI-R	106	0.03	16
S. aureus TET-R	48	0.06	>32
MRSA CLI-R	94	0.03	16
MRSA TET-R	31	0.06	>32
MSSA CLI-R	12	0.06	16
MSSA TET-R	17	0.06	>32
BHS	313	0.03	0.25
BHS AZI-R	82	0.06	0.5
BHS TET-R	121	0.06	0.5

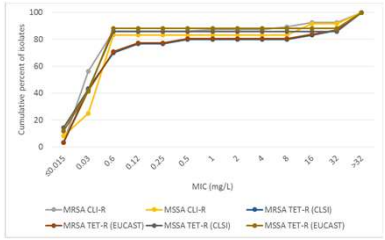
Clinical breakpoints used as per CLSI and EUCAST [4,5]

Figure 1: Cumulative percent iclaprim MIC distribution for *S. aureus* resistant to clindamycin/tetracycline



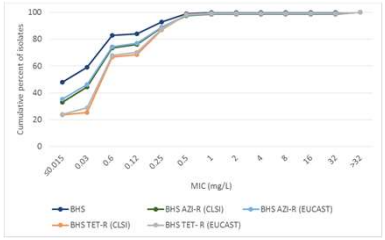
Clinical breakpoints used as per CLSI and EUCAST [4,5]

Figure 2: Cumulative percent iclaprim MIC distribution for MRSA and MSSA resistant to clindamycin/tetracycline



Clinical breakpoints used as per CLSI and EUCAST [4,5]

Figure 3: Cumulative percent iclaprim MIC distribution for beta-haemolytic streptococci resistant to macrolides/tetracycline



Clinical breakpoints used as per CLSI and EUCAST [4,5]

Conclusions

- Iclaprim was active against select skin and skin structure pathogens collected during 2015-2016 from Europe and North America. These included many isolates that were *S. aureus* resistant to clindamycin or tetracycline and beta-haemolytic streptococci isolates resistant to macrolides or tetracyclines.
- MIC_{50} were low for all phenotypes. MIC_{90} for all *S. aureus* was also low but several phenotypes showed higher MIC_{90}: however, frequency distribution plots confirmed that even against these isolates iclaprim exhibited activity against the majority of isolates tested
- Continued surveillance is warranted to monitor the activity of iclaprim against antibiotic resistant *S. aureus* and beta-haemolytic streptococci
- Further evaluation of isolates with MIC values >1 mg/L are warranted and likely require molecular characterization of iclaprim's target enzyme, dihydrofolate reductase.

References

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Contact

David Huang, MD, PhD
Motif BioSciences Inc.
5 Independence Way, Suite 300
Princeton, NJ 08540
david.huang@motifbio.com