Poster 60

# Surveillance of Iclaprim Activity: In Vitro Susceptibility of Gram-Positive Skin and Skin Structure Pathogens Collected During 2004-2016

**D. B. Huang**[1], S. Magnet[2], B. Lemos[2], C. Pillar[3], S. Hawser[2]

[1]Motif BioSciences, New York, NY, USA, [2]IHMA Europe Sàrl, Monthey, Switzerland,
[3]Micromyx, Kalamazoo, MI, USA

## ABSTRACT

**Background:** Iclaprim is a diaminopyrimidine inhibitor of bacterial dihydrofolate reductase (DHFR). In the present study, iclaprim, trimethoprim, and trimethoprim-sulfamethoxazole were tested against Gram-positive skin and skin structure pathogens, collected worldwide during 2004-2016.

**Methods:** 7,618 non-duplicative, non-consecutive isolates of *S. aureus* (N=6,312; MSSA and MRSA) and beta-hemolytic streptococci (N=1,306; *S. pyogenes, S. agalactiae, S. dysgalactiae*) underwent antibacterial susceptibility testing. Susceptibility testing was performed by broth microdilution in accordance with the Clinical and Laboratory and Standards Institute (CLSI) guidelines (CLSI M7).

**Results:** The activity of iclaprim, trimethoprim, and trimethoprim/sulfamethoxazole (MIC values reflect trimethoprim MIC of the combination) against Gram-positive skin pathogens by study period is shown in Table 1. Overall, iclaprim had potent and consistent activity against *S. aureus* and beta-hemolytic streptococci based on $MIC_{50/90}$ values observed across studies/time periods. Overall, resistance between species to trimethoprim-sulfamethoxazole was low and ranged from 0% to 3.9%; resistance to trimethoprim was less than 10% among *S. aureus* and was 10-13% among *S. agalactiae*.

**Conclusion:** Iclaprim was more active than trimethoprim alone and had similar activity to trimethoprim-sulfamethoxazole against Gram-positive clinical isolates collected from patients with skin and skin structure infections collected from 2004-2016 worldwide.

## INTRODUCTION

- Iclaprim is a novel diaminopyrimidine antibiotic, which inhibits bacterial dihydrofolate reductase, a critical enzyme in the bacterial folate synthesis pathway.
- Iclaprim is active against MRSA resistant to vancomycin or non-susceptible to linezolid or daptomycin [1].
- This evaluation presents the results of iclaprim, trimethoprim, and trimethoprim-sulfamethoxazole tested against Gram-positive skin and skin structure pathogens collected worldwide from 2004 to 2006, 2012 to 2014, and 2015 to 2016 [2,3].

## METHODS

Overall, there were 7,618 non-duplicative, non-consecutive isolates tested.
- Of the 6312 isolates of *S. aureus*, 2413 were methicillin-sensitive (MSSA) and 3899 were methicillin-resistant (MRSA).
- Of the 1306 isolates of beta-hemolytic streptococci, 861 were *S. pyogenes*, 405 *S. agalactiae*, and 40 *S. dysgalactiae.*

Antibacterial susceptibility testing was conducted by
- JMI Laboratories (North Liberty, Iowa, USA) for isolates from 2004-2006 and 2012-2014
- IHMA Europe Sàrl (Monthey, Switzerland) for isolates from 2015-2016.

Susceptibility testing was performed by broth microdilution in accordance with the Clinical and Laboratory and Standards Institute (CLSI) guidelines (M7-A7 [2006] and M07-A10 [2015]) [4,5].

Quality control and minimum inhibitory concentration (MIC) values were calculated using CLSI [6,7,8]
- M100-S18 [2008] for the 2004-2006 isolates
- M100-S25 [2015] for the 2012-2014 isolates
- M100-S27 [2017] for the 2015-2016 isolates.

## RESULTS

Isolates were collected from 2004 to 2006 (N=5324), 2012 to 2014 (N=1377) and 2015 to 2016 (N=917) from skin and skin structure infections, pneumonia, and blood stream infections. Geographic distribution of the isolates included:
- 49.5% North America
- 46.2% Europe
- 2.3% Asia-Pacific
- 2.0% South America.

The activity of iclaprim, trimethoprim, and trimethoprim/sulfamethoxazole against Gram-positive skin pathogens by study period is shown in Table 1.

Based on MIC values, iclaprim maintained consistent bactericidal activity throughout the 13 years from 2004 to 2016.
- The $MIC_{50/90}$ for iclaprim were 0.06/0.12, 0.06/0.12, and 0.03/0.06 µg/mL for 2004-2006, 2012-2014 and 2015-2016, respectively, for *S. aureus*.
- The $MIC_{50/90}$ for trimethoprim were 1/2 and 1/2 µg/mL, respectively, for 2004-2006 and 2012-2014 for *S. aureus*.
- The $MIC_{50/90}$ for trimethoprim-sulfamethoxazole were 0.06/0.12, 0.06/0.12, and ≤0.06/≤0.06 µg/mL, respectively, for 2004-2006, 2012-2014 and 2015-2016 for *S. aureus*.

## RESULTS

- The $MIC_{50/90}$ for iclaprim were 0.015/0.25, 0.06/0.25, and 0.03/0.25 µg/mL for 2004-2006, 2012-2014 and 2015-2016, respectively, for beta-hemolytic streptococci with similar results among its serotypes.
- The $MIC_{50/90}$ for trimethoprim were 0.25/2 and 1/2 µg/mL, respectively, for 2004-2006 and 2012-2014 for beta-hemolytic streptococci.
- The $MIC_{50/90}$ for trimethoprim-sulfamethoxazole were 0.06/0.12, 0.12/0.25, and ≤0.06/0.12 µg/mL, respectively, for 2004-2006, 2012-2014 and 2015-2016 for beta-hemolytic streptococci.

Resistance between species to trimethoprim-sulfamethoxazole was low and ranged from 0% to 3.9%.
- Resistance to trimethoprim was less than 10% among *S. aureus* isolates and was 10-13% among *S. agalactiae* isolates.

**Table 1. $MIC_{50/90}$ of iclaprim, trimethoprim and trimethoprim/sulfamethoxazole against Gram-positive clinical isolates collected worldwide during 2004-2016.**

| Organism | Year | N | Iclaprim | | Trimethoprim | | Trimethoprim/ Sulfamethoxazole* | |
|---|---|---|---|---|---|---|---|---|
| | | | $MIC_{50}$ | $MIC_{90}$ | $MIC_{50}$ | $MIC_{90}$ | $MIC_{50}$ | $MIC_{90}$ |
| *S. aureus* | 2004-2006 | 4516 | 0.06 | 0.12 | 1 | 2 | 0.06 | 0.12 |
| | 2012-2014 | 1178 | 0.06 | 0.12 | 1 | 2 | 0.06 | 0.12 |
| | 2015-2016 | 618 | 0.03 | 0.06 | - | - | ≤0.06 | ≤0.06 |
| MSSA | 2004-2006 | 1513 | 0.06 | 0.12 | 1 | 1 | 0.06 | 0.06 |
| | 2012-2014 | 596 | 0.06 | 0.12 | 1 | 2 | 0.06 | 0.06 |
| | 2015-2016 | 304 | 0.06 | 0.06 | - | - | ≤0.06 | ≤0.06 |
| MRSA | 2004-2006 | 3003 | 0.06 | 0.12 | 1 | 2 | 0.06 | 0.25 |
| | 2012-2014 | 582 | 0.06 | 0.5 | 1 | 8 | 0.06 | 0.25 |
| | 2015-2016 | 314 | 0.03 | 0.12 | - | - | ≤0.06 | 0.12 |
| β-hemolytic Streptococci | 2004-2006 | 808 | 0.015 | 0.25 | 0.25 | 2 | 0.06 | 0.12 |
| | 2012-2014 | 199 | 0.06 | 0.25 | 1 | 2 | 0.12 | 0.25 |
| | 2015-2016 | 299 | 0.03 | 0.25 | - | - | ≤0.06 | 0.12 |
| *S. pyogenes* | 2004-2006 | 604 | 0.015 | 0.03 | 0.25 | 0.5 | 0.06 | 0.12 |
| | 2012-2014 | 98 | 0.015 | 0.06 | 0.25 | 1 | 0.12 | 0.25 |
| | 2015-2016 | 159 | ≤0.015 | 0.03 | - | - | ≤0.06 | 0.12 |
| *S. agalactiae* | 2004-2006 | 204 | 0.12 | 0.25 | 1 | 4 | 0.06 | 0.12 |
| | 2012-2014 | 101 | 0.12 | 0.25 | 2 | 4 | 0.12 | 0.12 |
| | 2015-2016 | 100 | 0.12 | 0.5 | - | - | 0.12 | 0.12 |
| *S. dysgalactiae* | 2015-2016 | 40 | 0.03 | 0.06 | - | - | 0.03 | 0.06 |

*MIC value for trimethoprim shown.

## CONCLUSIONS

Iclaprim had consistent *in vitro* activity against Gram-positive clinical isolates including *S. aureus* (MSSA and MRSA) and beta-hemolytic streptococci collected from patients with skin and skin structure infections over 13 years from 2004 to 2016.

- Iclaprim was 8- to 32-fold more potent than trimethoprim alone and similar to that of trimethoprim-sulfamethoxazole against *S. aureus*, including MRSA, and beta-hemolytic streptococci from 2004 to 2016.

Iclaprim could be an important new therapeutic option for the treatment of ABSSSI caused by Gram-positive bacteria, including multi-drug resistant bacteria.

## REFERENCES

1. Huang DB, et al. Can J Infect Dis Med Microbiol. 2017.
2. Sader HS, et al. Antimicrob Agents Chemother. 2009.
3. Huang DB, et al. Diagn Microbiol Infect Dis. 2018.
4. CLSI. M07-A7. 2006.
5. CLSI. M07-A10. 2015.
6. CLSI. M100-S18. 2008.
7. CLSI. M100-S25. 2015.
8. CLSI. M100-S27. 2017.

## CONTACT

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