ABSTRACT

Background: Iclaprim (ICL) is a diaminopipridine derivative of bacterial dihydrofolate reductase. ICL and other antibiotics including standard of care regimens for ABSSSI are tested against the clinical isolates of Gram-positive pathogens from the two ABSSSI Phase 3 clinical studies, REVIVE-1 and REVIVE-2.

Methods: 802 isolates including S. aureus (MSSA and MRSA) (n=593), S. haemolyticus (n=1,432), beta-hemolytic streptococci (n=83), and viridans streptococci (n=113) collected at the baseline visit of the REVIVE-1 and REVIVE-2 studies underwent antibacterial susceptibility testing. Susceptibility testing was performed by broth microdilution according to Clinical and Laboratory Standards Institute (CLSI M07, 2018) methods. Quality control ranges and interpretive criteria for comparator compounds were as published (CLSI M100, 2018).

Results: A summary of the activity of ICL and comparator antibiotics for S. aureus, S. haemolyticus, beta-hemolytic streptococci, and viridans streptococci isolates are shown in Table 1. ICL MIC values for S. aureus including MSSA and MRSA were 16-fold lower than those for TMP and similar to TMP-SMX, ICL had greater potency than vancomycin, linezolid and daptomycin against MRSA. Based on MIC<sub>50/90</sub>, ICL was more potent than TMP and TMP-SMX against S. pyogenes, and the increased potency of ICL relative to TMP was consistent across the other tested beta-hemolytic streptococci. ICL MIC<sub>50/90</sub> values for S. anginosus group were up to 12-fold lower than those for TMP-SMX.

Conclusion: Iclaprim had potent activity by MIC<sub>50/90</sub> against S. aureus, including MSSA, S. haemolyticus, beta-hemolytic streptococci, and viridans streptococci in the Phase 3 REVIVE-1 and REVIVE-2 studies. ICL could be an important therapeutic option for the treatment of ABSSSI caused by Gram-positive bacteria.

INTRODUCTION

- Iclaprim is a novel diaminopipridine antibiotic, which inhibits bacterial dihydrofolate reductase, a critical enzyme in the bacterial folate synthesis pathway.
- Iclaprim is active against MRSA resistant to vancomycin or nonsusceptible to linezolid or daptomycin [1].
- In two Phase 3 clinical trials (REVIVE-1 and REVIVE-2) iclaprim has shown clinical response comparable to vancomycin among patients treated for ABSSSI [2,3].
- This evaluation provides an in vitro analysis of the antibiotics, including iclaprim, tested against the clinical isolates causing acute bacterial skin and skin structure infections from the two Phase 3 trials.

METHODS

- Overall, 1198 patients were included in the intent-to-treat population in the REVIVE-1 (n=598) and REVIVE-2 (n=600) ABSSSI clinical trials.
- 802 isolates causing skin and skin structure infections were collected at the baseline visit from the REVIVE-1 and REVIVE-2 patients from the United States (79.3%), Europe (20.4%), and Latin America (0.4%).
- 593 isolates of S. aureus, including 322 methicillin-susceptible and 272 methicillin-resistant
- 12 isolates of S. haemolyticus
- 83 isolates of beta-hemolytic streptococci
- 113 isolates of viridans streptococci
- Studies were conducted at IHMA, Montreal, Switzerland.
- Antibacterial susceptibility testing was performed by broth microdilution according to Clinical and Laboratory Standards Institute (CLSI M07, 2018) methods [4].
- Quality control ranges and interpretative criteria for comparator compounds were as published (CLSI M100, 2018) [5].

RESULTS

- The MIC<sub>50/90</sub> values of iclaprim, trimethoprim, trimethoprim-sulfamethoxazole, vancomycin, linezolid and daptomycin for all S. aureus, including methicillin-resistant (MRSA) and -susceptible (MSSA) strains, S. haemolyticus, beta-hemolytic streptococci, and viridans streptococci isolates are shown in Table 1.
- Iclaprim MIC<sub>50/90</sub> values were 0.06 and 0.12 µg/mL, respectively for S. aureus.
- TMP MIC<sub>50/90</sub> values were 1 and 2 µg/mL, respectively.
- TMP-SMX MIC<sub>50/90</sub> values were ≤0.12 and ≤0.12 µg/mL, respectively.
- For MRSA, iclaprim had increased potency with MIC<sub>50/90</sub> Values of 0.03 and 0.25 µg/mL compared with TMP (0.5 and 4 µg/mL), and similar MIC<sub>50/90</sub> values to TMP-SMX (both ≤ 0.12 µg/mL).
- Iclaprim had greater potency than vancomycin (8-fold), linezolid (16-fold) and daptomycin (4-fold) against MRSA.
- Increased potency of iclaprim relative to TMP was consistent across the tested beta-hemolytic streptococci
- Based on MIC<sub>50/90</sub>, iclaprim was more potent than TMP (4-fold) and TMP-SMX (2-fold) against S. pyogenes with MIC<sub>50/90</sub> values of 0.015 and 0.12 µg/mL, respectively.
- Iclaprim MIC<sub>50/90</sub> for the isolates in the S. anginosus group were ≤0.004 and 0.008 µg/mL, respectively. MIC<sub>50/90</sub> values for TMP and TMP-SMX were ≤0.12/≤0.12 µg/mL and ≤0.06/0.06 µg/mL, respectively.

CONCLUSIONS

- Iclaprim MIC distribution between Europe, including Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Portugal, Romania, Turkey, Ukraine and Belgium, and the United States was similar in the REVIVE studies (Figure 1).
- Iclaprim MIC distribution for Gram-positive pathogens in Europe and the US*

REFERENCES


CONTACT

Stephanie Noviello, MD, MPH
Motif BioSciences Inc.
5 Independence Way, Suite 300
Princeton, NJ 08540
Stephanie.noviello@motifbio.com