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Surveillance of Iclaprim Activity against Multi-Drug Resistant Streptococci Collected from Patients with Skin and Skin Structure Infections from 2013-2017 from Locations Worldwide

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Abstract

Introduction: More than 80% of skin and skin structure infections are caused by Gram-positive bacteria, and antibiotic resistance is a growing public health concern for some of these pathogens. Iclaprim, a dihydrofolate reductase (DHFR) inhibitor, is being developed to treat Gram-positive infections, including acute bacterial skin and skin structure infections (ABSSSI) due to multidrug resistant bacteria.

Methods: Clinical isolates of *S. pyogenes* (n=204), *S. agalactiae* (n=122), *S. constellatus* (n=106), *S. anginosus* (n=101), *S. dysgalactiae* (n=39), *S. intermedius* (n=11) were investigated. Isolates were collected globally between 2013 to 2017 from patients with skin and skin structure infections. Iclaprim was tested along with multiple comparator antibiotics against *Streptococcus* species including strains with multi-resistance to azithromycin, clindamycin and tetracycline. Susceptibility testing was performed by broth microdilution in accordance with the CLSI guidelines. Minimum inhibitory concentration (MIC) interpretations were based on CLSI breakpoints (except for iclaprim where no breakpoints are available to date).

Results: Of the 583 clinical isolates, 44 (7.5%) isolates had co-resistance to azithromycin, clindamycin and tetracycline. Of these, 18 (40.9%) were collected from Europe, 16 (36.4%) from the USA and 10 (22.7%) from rest of the world. Iclaprim and other comparators' MIC_{90} for the *Streptococcus* species are shown in Table 2. The iclaprim MIC_{90} for all of the *Streptococcus* species' isolates was 0.25 µg/ml and the MIC_{90} for the isolates with multidrug resistance was 0.5 µg/ml.

Conclusions: Iclaprim exhibited potent activity against all streptococci isolates, including those with multidrug resistance to azithromycin, clindamycin and tetracycline collected from 2013 through 2017. Continued surveillance is warranted to monitor the activity of iclaprim against streptococci as well as to detect any emergence of resistance.

*Minor modifications made to abstract.

Introduction

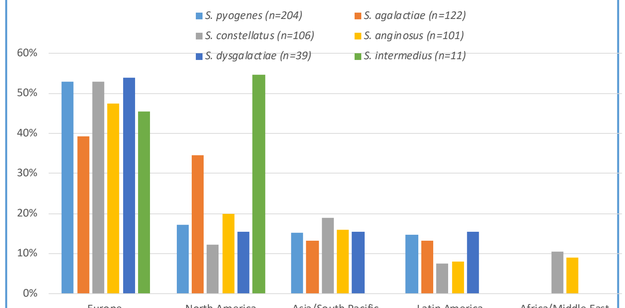
- More than 80% of skin and skin structure infections are caused by Gram-positive bacteria.
- Antibiotic resistance is a growing public health concern for some of the pathogens causing skin and skin structure infections.
- Iclaprim is a novel next generation diaminopyrimidine antibiotic, which inhibits bacterial dihydrofolate reductase, a critical enzyme in the bacterial folate synthesis pathway.
- Iclaprim has a targeted Gram(+) spectrum of activity and is active against MRSA resistant to vancomycin or non-susceptible to linezolid or daptomycin.[1]
- In two Phase 3 clinical trials (REVIVE-1 and REVIVE-2) iclaprim has shown early clinical response at an early time point comparable to vancomycin among patients treated for acute bacterial skin and skin structure infections (ABSSSI).[2,3]
- The current study provides an *in vitro* analysis of iclaprim and comparator antibiotics against *Streptococcus* species
  - Collected from patients with skin and skin structure infections in 2013-2017 globally.
  - Isolates include those with multi-drug resistance to azithromycin, clindamycin and tetracycline.

Methods

- Iclaprim was tested along with multiple comparator antibiotics against *Streptococcus* species including strains with multi-drug resistance to azithromycin, clindamycin and tetracycline.
- 583 isolates were collected from patients with skin and skin structure infections
  - 204 isolates of *S. pyogenes*
  - 122 isolates of *S. agalactiae*
  - 106 isolates of *S. constellatus*
  - 101 isolates of *S. anginosus*
  - 39 isolates of *S. dysgalactiae*
  - 11 isolates of *S. intermedius*
- Isolates were collected globally with the majority from Europe (49%) and the USA (21%) between 2013-2017.
- Studies were conducted at IHMA Europe Sàrl, Monthey, Switzerland.
- Antibacterial susceptibility testing was performed by broth micro-dilution according to Clinical and Laboratory Standards Institute methods.[4]
- Minimum inhibitory concentration (MIC) interpretations were based on CLSI breakpoints, except for iclaprim where breakpoints are yet to be established.[5]

Results

Figure 1. Distribution of *Streptococcus* spp. isolates by region.



Results

- The distribution of isolates by region is shown in Figure 1; most isolates had an iclaprim MIC of 0.03 µg/ml or lower.
- Iclaprim MIC_{90} for all *Streptococcus sp.* isolates are shown in Table 1.
- In addition, the MIC_{90} values of ampicillin, azithromycin, ceftriaxone, clindamycin, penicillin, tetracycline, trimethoprim-sulfamethoxazole are listed.
- Iclaprim MIC_{90} were either lower or similar to most of the comparators including trimethoprim-sulfamethoxazole.

Table 1. MIC_{90} (µg/ml) distribution for iclaprim and comparator antibiotics for *Streptococcus* species (2013-2017).

Organism	ICL	AMP	AZI	CRO	CLI	PEN	TET	TMP/SMX
S. pyogenes (n=204)	0.03	≤0.03	>2	0.03	0.06	≤0.06	>8	0.25
S. agalactiae (n=122)	0.5	0.12	>2	0.12	>1	≤0.06	>8	0.25
S. constellatus (n=106)	≤0.004	0.25	>2	0.5	>1	≤0.06	>8	≤0.06
S. anginosus (n=101)	≤0.004	0.12	>2	0.25	>1	≤0.06	>8	≤0.06
S. dysgalactiae (n=39)	0.12	≤0.03	>2	0.03	0.25	≤0.06	>8	0.25
S. intermedius (n=11)	0.008	0.06	>2	0.12	0.06	≤0.06	4	≤0.06

Abbreviations: AMP, ampicillin; AZI, azithromycin; CRO, ceftriaxone; CLI, clindamycin; ICL, iclaprim; PEN, penicillin; TET, tetracycline; TMP/SMX, trimethoprim-sulfamethoxazole.

- Of the 583 clinical isolates, 44 (7.5%) isolates were multi-drug resistant (resistant to azithromycin, clindamycin and tetracycline) (Table 2).
  - 18 (40.9%) were collected from Europe, 16 (36.4%) from the USA and 10 (22.7%) from rest of the world.
- The iclaprim MIC_{90} for all of the *Streptococcus* species was 0.25 µg/ml and the MIC_{90} for the isolates with multi-drug resistance was 0.5 µg/ml.

Results

Table 2. MIC_{90} (µg/ml) distribution for iclaprim and comparator antibiotics for *Streptococcus* species with multi-drug resistance (2013-2017).

Antibiotic	*S. agalactiae* (n=29)	*S. anginosus* (n=10)	*S. pyogenes* (n=5)*
Iclaprim	0.5	≤0.004	≤0.004-0.015
Ampicillin	0.12	0.12	≤0.03-≤0.03
Azithromycin	>2	>2	>2->2
Ceftriaxone	0.12	0.25	≤0.015-0.03
Clindamycin	>1	>1	>1->1
Penicillin	≤0.06	≤0.06	≤0.06-≤0.06
Tetracycline	>8	>8	>8->8
Trimethoprim/Sulfamethoxazole	0.25	≤0.06	≤0.06-0.12

*Range provided since MIC_{90} not calculable with n < 10.

Conclusions

- Iclaprim exhibited potent activity against all 583 Streptococci isolates, including 44 (7.5%) with multidrug resistance to azithromycin, clindamycin and tetracycline collected from 2013 through 2017 from locations worldwide.
- Continued surveillance is warranted to monitor the activity of iclaprim against streptococci as well as to detect any potential emergence of resistance.

References

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