Iclaprim is a novel dihydrofolate reductase inhibitor belonging to the diaminopyrimidine class of antibiotics for which trimethoprim (TMP) is the most well-known representative. TMP is frequently used in combination with sulfamethoxazole (SMX) and this combination has been used in clinical practice for almost five decades. SMX is highly synergistic with TMP as a result of inhibition of two sequential enzymes in the folate pathway. Thus, the potency and bactericidal activity as well as reducing the potential for resistance development. Moreover, SMX is often associated with allergy reactions. In contrast, iclaprim by itself shows a potent activity against a variety of pathogens and exhibit a potent bactericidal action against methicillin-resistant and susceptible Staphylococcus aureus, Streptococcus pneumoniae and important respiratory tract infection (RTI) pathogens.

A recent broad clinical trial showed that in healthy subjects the concentrations of iclaprim in the epithelial lining fluid and alveolar macrophages were about 20 and 40 times higher than in plasma, respectively.

In the present study, we evaluated the in-vitro activity of iclaprim tested against Enterobacteriaceae strains collected from North American (United States [USA]) and European medical centers as part of the International Study on Iclaprim Susceptibility (ISIS) surveillance program.

**METHODS**

**Bacterial strains.** A total of 312 clinical strains were evaluated: 107 E. coli (54 from USA and 53 from European medical centers); 104 Klebsiella pneumoniae (55 from USA and 54 from European medical centers); and 10 Enterobacter sakazakii (6 from USA and 4 from European medical centers). Of organisms collected between 2004 and 2006. Sources of infection consisted of blood, skin and soft tissue, respiratory and patients hospitalized from pneumonia.

**Susceptibility testing.** MIC values were evaluated by Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (M7-A7 [2007]). The broth microdilution plates were read with a CLSI MicroWell Scan automated reader (CLSI). To ensure in vitro testing, susceptibility results were compared for compounds and quality control ranges for all compounds were those published in the M100-S17 document (2007).

**RESULTS**

- Iclaprim exhibited good activity against Enterobacteriaceae with an overall MIC
distribution of 0.12 μg/mL (Table 1).
- Similar ICL MIC distributions and S rates for trimethoprim (TMP) and co-trimoxazole (TMP/SMX) were observed in the USA and in Europe.
- Similar potency and bactericidal activity as well as reducing the potential for resistance development.
- In the presented study, we evaluated the in-vitro activity of iclaprim tested against Enterobacteriaceae strains collected from North American United States (USA) and European medical centers as part of the International Study on Iclaprim Susceptibility (ISIS) surveillance program.

**REFERENCES**

1. R.N. Jones, T.R. Fritsche, K. Islami, S. Hawser, H.S. Sader. Iclaprim exhibited good activity against many strains of E. coli, K. pneumoniae and Enterobacter spp. with an overall MIC50 against the Enterobacteriaceae species in this study of 2 μg/mL.
2. Based on the rapid and extensive distribution of iclaprim into key compartments of the lungs, studies aimed at assessing the clinical utility of iclaprim in the treatment of pneumonia infections caused by these pathogens may be warranted.

**CONCLUSIONS**

Iclaprim exhibited good activity against many strains of E. coli, K. pneumoniae and Enterobacter spp. with an overall MIC50 against the Enterobacteriaceae species in this study of 2 μg/mL. Based on the rapid and extensive distribution of iclaprim into key compartments of the lungs, studies aimed at assessing the clinical utility of iclaprim in the treatment of pneumonia infections caused by these pathogens may be warranted.

**Table 1.** Activity of iclaprim and comparator agents tested against Enterobacteriaceae from the USA and Europe.

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</table>

**DISCUSSION**

Iclaprim is a novel dihydrofolate reductase, iclaprim, tested against clinical strains of Enterobacteriaceae: results from the International Study of Iclaprim Susceptibility (ISIS)

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**ABSTRACT**

Background: Iclaprim (ICL) is a diaminopyrimidine compound for IV and PO use, with promising activity against Gram-negative organisms. The activity of ICL was tested against clinical strains of ENT collected in the USA and EU in 2005 to further define its Gram-negative spectrum.

Methods: 312 strains from the USA (154) and Europe (158) were susceptibilities (S) tested by CLSI broth microdilution method against ICL and 12 comparators. All Enterobacteriaceae (ENT) strains were collected from bloodstream infections (BSI) in 47 hospitals located in the USA (23) and EU (24 in 12 countries).

Results: ICL was more active against E. coli and P. aeruginosa (MIC50 0.5 μg/mL) compared to E. cloacae (MIC4 4 μg/mL), see Table. Similar ICL MIC distributions and S rates for trimethoprim (TMP) and co-trimoxazole (TMP/SMX) were observed in the USA compared to EU. Overall S rates were 56% for TMP and 65% for TMP/SMX, varying from 63% and 64% among E. coli to 71 and 72% among E. cloacae, respectively. Among E. coli, rates of definitive or presumptive (CP) resistance (R) and ESBL phenotypes, respectively, were 15 and 5% in the USA and 20 and 9% in EU, while among E. pneumoniae CIP-R varied from 6% (USA) to 10% (EU) and the prevalence of ESBL phenotype was 18% in the USA and 22% in EU. For ceftazidime (CAZ) was observed in 24% of E. cloacae in the USA and higher in EU/S9.

Conclusions: Overall, ICL (MIC50 0.5 μg/mL) activity against ENT was only slightly less than that of TMP (MIC50 0.5 μg/mL), which demonstrated a spectrum (99% S) comparable to TMP/SMX (99%) and ceftazidime (97%), but superior to amoxicillin/clavulanate (51%) and ceftazidime (54%).

**INTRODUCTION**

Iclaprim is a novel investigational drug that is being developed for various Gram-negative bacterial infections. The compound has been granted fast track product designation and has recently completed two pivotal Phase II clinical studies in complicated skin and skin structure infections (cSSSI).

**RESULTS**

- Iclaprim exhibited good activity against Enterobacteriaceae with an overall MIC<sub>50</sub> of 2 μg/mL and MIC<sub>90</sub> against Escherichia coli, K. pneumoniae and Enterobacter spp. of 6, 2, 4 μg/mL, respectively (Table 1).  
- TMP/SMX combination (MIC<sub>50</sub> 0.12 μg/mL) was four to eightfold more active than TMP alone (MIC<sub>50</sub> 0.5–1 μg/mL), which in turn was fourfold more active than iclaprim (MIC<sub>50</sub> 5–4 μg/mL). Sensitivity rates for TMP/SMX and TMP were overall very similar against the Enterobacteriaceae species evaluated, which only varied from 62.6% to 63.6% for CAZ among those from Europe for most antimicrobial agents tested.

**DISCUSSION**

Iclaprim exhibited good activity against many strains of E. coli, K. pneumoniae and Enterobacter spp. with an overall MIC<sub>50</sub> against the Enterobacteriaceae species in this study of 2 μg/mL. Based on the rapid and extensive distribution of iclaprim into key compartments of the lungs, studies aimed at assessing the clinical utility of iclaprim in the treatment of pneumonia infections caused by these pathogens may be warranted.