Antimicrobial activity of 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 expanded activity against Gram-positive and -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 (EU, 158) were susceptibility (S) tested by CLSI broth microdilution method against ICL and 12 comparators. All Enterobacteriaceae (ENT) strains were collected from bloodstream infections in 47 hospitals located in the USA (23) and EU (24 in 12 countries).

Results: ICL was more active against *E. coli* and *K. pneumoniae* (MIC_{50}, 2 µg/mL) compared to *E. cloacae* (MIC_{50}, 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 68% for TMP and 69% for TMP/SMX, varying from 63 and 64% among *E. coli* to 71 and 72% among *E. cloacae*, respectively. Among *E. coli*, rates of ciprofloxacin (CIP) resistance (R) and ESBL phenotype, respectively, were 15 and 5% in the USA and 20 and 9% in EU; while among *K. pneumoniae* CIP-R varied from 6 (USA) to 19% (EU) and the prevalence of ESBL phenotype was 18% in the USA and 32% in EU. R to ceftazidime (CAZ) was observed in 24% of *E. cloacae* in the USA and higher in EU (39%).

	Cumulative % inhibited at ICL MIC (µg/mL) of :				
Organism (no.)	≤0.5	1	2	4	8
E. coli (107)	12	39	57	62	63
K. pneumoniae (104)	0	10	54	60	66
E. cloacae (101)	0	10	47	62	70

Conclusions: Overall, ICL (MIC_{50}, 2 µg/mL) activity against ENT was only slightly less than that of TMP (MIC_{50}, 0.5 µg/mL) which demonstrated a spectrum (68% S) comparable to TMP/SMX (69%) and cefuroxime (67%), but superior to amoxicillin/clavulanate (51%) and cefazolin (54%).

INTRODUCTION

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

Iclaprim is a novel dihydrofolate reductase (DFHR) 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, thereby enhancing the potency and bactericidal activity as well as reducing the potential for resistance development. However, SMX is often associated with allergic reactions. In contrast, iclaprim by itself shows a potent activity against a variety of pathogens and exhibits a potent bactericidal action against methicillin-susceptible and -resistant *Staphylococcus aureus*, *Streptococcus pneumoniae* and important respiratory tract infection (RTI) pathogens.

A recent bronchial alveolar lavage study 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 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.

METHODS

Bacterial isolates: A total of 312 clinical strains were evaluated, 107 *E. coli* (54 from USA and 53 from European medical centers), 104 *Klebsiella pneumoniae* (50 from USA and 54 from European medical centers) and 101 *Enterobacter cloacae* (50 from USA and 51 from European medical centers). All organisms were collected between 2004 and 2006. Sources of infection consisted of bloodstream, skin and soft tissue, respiratory and patients hospitalized from pneumonia.

Susceptibility testing: MIC values were evaluated by Clinical and Laboratory Standards Institute (CLSI, formerly the NCCLS) broth microdilution method per M7-A7 [2006]. Interpretive criteria for comparator 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_{50} of 2 µg/mL and MIC_{50}s against *Escherichia coli*, *K. pneumoniae* and *Enterobacter* spp. of 2, 2 and 4 µg/mL, respectively (Table 1).
- TMP/SMX combination (MIC_{50}, 0.12 µg/mL) was four- to eight-fold more active than TMP alone (MIC_{50}, 0.5–1 µg/mL), which in turn was four-fold more active than iclaprim (MIC_{50}, 2–4 µg/mL). Susceptibility 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 *E. coli*, from 70.2 to 72.1% for *K. pneumoniae*, and from 71.3 to 72.3% for *Enterobacter* spp.(Table 1).
- In general, isolates from the USA showed susceptibility rates slightly higher than those from Europe for most antimicrobial agents tested.

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

Organism (no.tested)/ Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
***E. coli* (107)**				
Iclaprim	2	>8	0.25–>8	- / -[b]
Trimethoprim	0.5	>64	0.12–>64	62.6 / 37.4
Trimethoprim/sulfamethoxazole	0.12	>8	0.03–>8	63.6 / 36.4
Amoxicillin/clavulanic acid	8	32	≤1–>32	70.1 / 13.1
Cefazolin	2	16	≤1–>32	83.2 / 8.4
Cefuroxime	4	16	≤1–>32	89.7 / 6.5
Cefuroxime	≤1	≤1	≤1–>32	94.4 / 5.6 (5.6)[c]
Ceftazidime	≤1	≤1	≤1–>16	95.3 / 3.7 (6.5)[c]
Gentamicin	≤0.5	1	≤0.5–>16	94.4 / 5.6
Tetracycline	≤2	>16	≤2–>16	72.9 / 27.1
Levofloxacin	≤0.12	>4	≤0.12–>4	82.2 / 17.8
***K. pneumoniae* (104)**				
Iclaprim	2	>8	1–>8	- / -[b]
Trimethoprim	0.5	>64	0.25–>64	70.2 / 29.8
Trimethoprim/sulfamethoxazole	0.12	>8	0.03–>8	72.1 / 27.9
Tetracycline	≤2	>16	≤2–>16	78.8 / 21.2
Levofloxacin	≤0.12	>4	≤0.12–>4	88.5 / 10.6
Amoxicillin/ clavulanic acid	4	16	≤1–>32	77.9 / 8.7
Cefazolin	2	>32	≤1–>32	73.1 / 25.0
Cefuroxime	2	>32	≤1–>32	75.0 / 19.2 (23.1)[c]
Ceftriaxone	≤1	>32	≤1–>32	76.9 / 14.4 (24.0)[c]
Ceftazidime	≤1	>16	≤1–>16	81.7 / 14.4
Gentamicin	≤0.5	>16	≤0.5–>16	85.6 / 14.4
***Enterobacter* spp. (101)**				
Iclaprim	4	>8	1–>8	- / -[b]
Trimethoprim	1	>64	0.25–>64	71.3 / 28.7
Trimethoprim/sulfamethoxazole	0.12	>8	0.06–>8	72.3 / 27.7
Tetracycline	≤2	>16	≤2–>16	72.3 / 21.8
Levofloxacin	≤0.12	>4	≤0.12–>4	84.2 / 11.9
Amoxicillin/clavulanic acid	>32	>32	≤1–>32	3.0 / 93.1
Cefazolin	>32	>32	2–>32	2.0 / 97.0
Cefuroxime	32	>32	≤1–>32	35.6 / 52.5
Ceftriaxone	≤1	>32	≤1–>32	62.4 / 25.7
Ceftazidime	≤1	>16	≤1–>16	64.4 / 31.7
Gentamicin	≤0.5	>16	≤0.5–>16	82.2 / 15.8
All Enterobacteriaceae (312)				
Iclaprim	2	>8	0.25–>8	- / -[b]
Trimethoprim	0.5	>64	0.12–>64	67.9 / 32.1
Trimethoprim/sulfamethoxazole	0.12	>8	0.03–>8	69.2 / 30.8
Tetracycline	≤2	>16	≤2–>16	74.7 / 23.4
Levofloxacin	≤0.12	>4	≤0.12–>4	84.9 / 13.5
Amoxicillin/clavulanic acid	8	>32	≤1–>32	51.0 / 37.5
Cefazolin	8	>32	≤1–>32	53.5 / 42.6
Cefuroxime	4	>32	≤1–>32	67.3 / 25.6
Ceftriaxone	≤1	>32	≤1–>32	78.2 / 15.1
Ceftazidime	≤1	>16	16	80.8 / 16.3
Gentamicin	≤0.5	>16	≤0.5–>16	87.5 / 11.9

[a] Criteria as published by the CLSI [2006].
[b] - = No criteria have been established by the CLSI [2007].
[c] Percentage of isolates with ESBL phenotype (MIC ≥2 µg/mL). [CLSI, 2007]

CONCLUSIONS

- **Iclaprim exhibited good activity against many strains of *E. coli*, *K. pneumoniae* and *Enterobacter* spp. with an overall MIC_{50} 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.**

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