In Vitro Activity of KPI-10 Tested Against a Global Collection of *Acinetobacter* spp. Including Multi-Drug Resistant (MDR) Strains

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Abstract

Background: KPI-10 (WQ-3813) is a novel fluoroquinolone (FQ) with potent broad-spectrum activity against Gram-positive and -negative bacteria including select FQ-resistant strains. In this study, KPI-10 and comparators were evaluated against a global collection of *Acinetobacter* spp. (AB) including MDR strains.

Methods: 213 MDR-AB collected from medical centers in North America, Europe, Latin America, and Asia-Pacific were selected based on resistance to at least 3 of the following agents: ciprofloxacin, meropenem, piperacillin/tazobactam, ceftazidime and gentamicin. 65 oxacillinase-producing AB (OXA-23/OXA-24/OXA-58; 36/12/17 strains) were also selected from the four regions. MIC values were determined using reference CLSI broth microdilution methods. QC organisms and interpretive criteria for comparator compounds were those recommended by CLSI.

Results: 100 (47.0%) of the isolates were from bloodstream, 94 (44.1%) from respiratory tract, 8 (3.8%) from skin/skin structure, and 11 (5.2%) from an unknown infection site. KPI-10 and tigecycline were the most potent agents against the 213 AB, exhibiting a MIC_{90} value of 2 µg/ml. All other agents had $MIC_{50/90}$ values of >8 µg/ml. The MIC_{90} values for KPI-10 and tigecycline for 65 OXA-producing AB were identical at 2 µg/ml, compared to >8 µg/ml for all other agents. All 213 MDR-AB isolates and 63/65 (96.9%) of the oxacillinase-producing AB were ciprofloxacin-resistant. 209/213 (98.1%) of the MDR-AB and 63/65 (96.9%) of the oxacillinase-producing AB isolates had KPI-10 MIC ≤4 µg/ml.

Conclusions: KPI-10 demonstrated potent activity against a collection of MDR-AB and oxacillinase-producing isolates. It was the only FQ to exhibit an on-scale MIC_{90} value (2 µg/ml); the strains were highly resistant to comparators (MIC_{90} >8 µg/ml). KPI-10's overall potent activity against MDR-AB suggests that it merits further evaluation for its potential to address serious hospital infections where MDR-AB may be a concern.

Introduction

The rising incidence of multidrug-resistance (MDR) in *Acinetobacter* spp. has become a serious problem in the management of serious hospital-acquired infections. *Acinetobacter* spp. may develop resistance to multiple broad-spectrum antimicrobial agents, including fluoroquinolones, aminoglycosides, and cephalosporins. The use of carbapenems, glycylcyclines, combination therapies or "agents of last resort", such as the polymyxins, has become more commonplace in an effort to treat serious infections due to these MDR pathogens.

Fluoroquinolones are one of most widely used antimicrobial classes. However, along with the increased use of this class, resistance to these agents has increased. For example, in a large surveillance study published by Lockhart et al. in 2007, which was conducted between 1993 and 2004, resistance rates in *Acinetobacter* spp. increased most dramatically to ciprofloxacin; the percentage of fluoroquinolone-susceptible *Acinetobacter* strains dropped from 61.5% to 35.2% over the 12 year duration of the study. Resistance to fluoroquinolones may occur due to mutations in the target enzymes (DNA gyrase and topoisomerase IV), decreased permeation of drug into the bacterial cell, or active efflux of the drug.

KPI-10 (formerly WQ-3813, the maleic acid salt of WQ-3810) is a novel broad spectrum fluoroquinolone containing a 6-amino-3,5-difluoropyridine at the 1-position and 3-isopropylaminoazetidine at the 7-position which has potent activity against Gram-positive and -negative bacteria including select drug-resistant strains. In this study, KPI-10 and comparator fluoroquinolones were evaluated against a global collection of *Acinetobacter* spp. including MDR strains.

Materials & Methods

MDR-*Acinetobacter* spp. were selected based on resistance to at least 3 of the following agents: ciprofloxacin, meropenem, piperacillin/tazobactam, ceftazidime or gentamicin. This collection included 213 isolates all of which were ciprofloxacin-resistant collected during 2010 from North America (NA,102 isolates), Latin America (LA, 32 isolates), Europe (EU, 49 isolates) and Asia-Pacific (APAC, 30 isolates). The isolates consisted of 100 (47.0%) from bloodstream, 94 (44.1%) from respiratory tract, 8 (3.8%) from skin/skin structure, and 11 (5.2%) from unknown sites of infection. Oxacillinase (OXA)-producing strains of *Acinetobacter* spp. (65 isolates; 96.9% ciprofloxacin-resistant) with previously identified genotypes were selected from all four regions and included OXA-23 (36 strains), OXA-24 (12 strains) and OXA-58 (17 strains). The OXA-producing isolates consisted of 37 (56.9%) from bloodstream, 23 (35.4%) from respiratory tract, and 5 (7.7%) from skin/skin structure infections.

KPI-10 antimicrobial powder was provided by Kalidex. The antimicrobial powder was dissolved in distilled water to make a stock solution for testing of 1280 µg/ml. Comparator agent powder lots were provided by JMI Laboratories through Sigma-Aldrich or respective manufacturers. Antimicrobials tested were KPI-10, ciprofloxacin, levofloxacin, moxifloxacin, gatifloxacin, ceftazidime, cefepime, meropenem, piperacillin/tazobactam, amikacin, and tigecycline. MIC values were determined using the reference Clinical and Laboratory Standards Institute (CLSI) broth microdilution method as described in M07-A9 [2012]. Reference frozen-form assay panels were produced by JMI Laboratories (North Liberty, Iowa, USA) and consisted of cation-adjusted Mueller-Hinton broth (MHB). Quality control (QC) ranges and interpretive criteria for comparator compounds were as published in CLSI M100-S22 [2012]. The tested QC strain was *P. aeruginosa* ATCC 27853. All QC results were within CLSI established ranges.

Results

- KPI-10 and tigecycline were the most potent agents against MDR *Acinetobacter* spp. (n=213), both with a MIC_{90} value at 2 µg/ml (Tables 1 and 2). All other agents had $MIC_{50/90}$ values at >8 µg/ml. Susceptibility rates for other fluoroquinolones, ceftazidime, cefepime, meropenem, and piperacillin-tazobactam were <10.0%; amikacin susceptibility was 24.9% (Table 2).
- In the North American subset of the collection (n=102), the MIC_{90} values for KPI-10 and tigecycline were 4 µg/ml (Table 2). Susceptibility rates for other fluoroquinolones, ceftazidime, cefepime, meropenem, and piperacillin-tazobactam were <10.0%; amikacin susceptibility was 25.5%.
- The MIC_{90} for KPI-10 and tigecycline for the collection of OXA-producing *Acinetobacter* spp. (n=65) were identical when compared to the MDR collection of *Acinetobacter* spp., i.e., MIC_{90s} were 2 µg/ml for KPI-10 and tigecycline and >8 µg/ml for all other agents (Table 3). Susceptibility rates for fluoroquinolones other than KPI-10, ceftazidime, cefepime, meropenem, piperacillin-tazobactam were <10.0%; amikacin susceptibility was 15.4% (Table 3).
- There were only six *Acinetobacter* strains with KPI-10 MIC values ≥8 µg/ml; five strains were at 8 µg/ml and one was at >8 µg/ml. Four of these strains were from the global MDR- *Acinetobacter* spp. collection and two were from the OXA-producing *Acinetobacter* spp. collection. Each of these strains was resistant to fluoroquinolones other than KPI-10.
- All 213 of the MDR- *Acinetobacter* spp. isolates and 96.9% of the OXA-producing *Acinetobacter* spp. were ciprofloxacin-resistant.

Table 1. MIC frequency distributions and cumulative percent inhibited for KPI-10 and comparator fluoroquinolone antimicrobial agents tested against MDR- and OXA-producing strains of *Acinetobacter* spp.

Organism/ antimicrobial agent (no. tested)	No. (cumulative %) of isolates inhibited at antimicrobial MIC (µg/ml): ≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8	MIC_{50}	MIC_{90}
MDR-*Acinetobacter* spp. (213)															
KPI-10	-[a]	-	-	-	-	-	7 (3.3)	49 (26.3)	76 (62.0)	60 (90.1)	17 (98.1)	3 (99.5)	1 (100.0)	1	2
Ciprofloxacin	-	-	-	-	-	-	-	-	-	-	-	-	213 (100.0)	>8	>8
Levofloxacin	-	-	-	-	-	-	-	-	-	-	17 (8.0)	59 (35.7)	137 (100.0)	>8	>8
Moxifloxacin	-	-	-	-	-	-	-	-	-	3 (1.4)	14 (8.0)	51 (31.9)	145 (100.0)	>8	>8
Gatifloxacin	NT[b]	NT	NT	NT	-	-	-	-	-	3 (1.4)	16 (8.9)	72 (42.7)	122 (100.0)	>8	>8
OXA-producing *Acinetobacter* spp. (65)															
KPI-10	-	-	1 (1.5)	1 (3.1)	0 (3.1)	0 (3.1)	2 (6.2)	13 (26.2)	28 (69.2)	16 (93.9)	2 (96.9)	2 (100.0)	-	1	2
Ciprofloxacin	-	-	-	-	1 (1.5)	1 (3.1)	0 (3.1)	0 (3.1)	0 (3.1)	0 (3.1)	0 (3.1)	0 (3.1)	63 (100.0)	>8	>8
Levofloxacin	-	-	-	-	1 (1.5)	1 (3.1)	0 (3.1)	0 (3.1)	0 (3.1)	0 (3.1)	2 (6.2)	26 (46.2)	35 (100.0)	>8	>8
Moxifloxacin	-	-	-	1 (1.5)	1 (3.1)	0 (3.1)	0 (3.1)	0 (3.1)	1 (4.6)	0 (4.6)	4 (10.8)	18 (38.5)	40 (100.0)	>8	>8
Gatifloxacin	NT	NT	NT	NT	2 (3.1)	0 (3.1)	0 (3.1)	0 (3.1)	0 (3.1)	2 (6.2)	7 (16.9)	27 (58.5)	27 (100.0)	8	>8

a. A dash indicates that no values were observed at that MIC value.
b. NT = dilution was not tested.

Table 2. Activity of KPI-10 and comparator antimicrobial agents when tested against 213 isolates of MDR-*Acinetobacter* spp.[a] (all regions).

Organism/ antimicrobial agent (no. tested)	MIC (µg/ml) MIC_{50}	MIC_{90}	Range	CLSI[b] %S / %R	EUCAST[b] %S / %R
Acinetobacter spp. (**All regions**, 213)					
KPI-10	1	2	0.25 – >8	- / -	- / -
Ciprofloxacin	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Levofloxacin	>8	>8	4 – >8	0.0 / 92.0	0.0 / 100.0
Moxifloxacin	>8	>8	2 – >8	- / -	- / -
Gatifloxacin	>8	>8	2 – >8	1.4 / 91.1	- / -
Ceftazidime	>16	>16	8 – >16	0.9 / 95.3	- / -
Cefepime	>16	>16	16 – >16	0.0 / 98.1	- / -
Meropenem	>8	>8	1 – >8	9.9 / 87.3	6.6 / 87.3
Piperacillin/tazobactam	>64	>64	64 – >64	0.5 / 99.5	- / -
Amikacin	>64	>64	1 – >64	24.9 / 63.4	21.1 / 75.1
Tigecycline[c]	1	2	0.06 – >4	- / -	- / -
North America (102)					
KPI-10	1	4	0.25 – 8	- / -	- / -
Ciprofloxacin	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Levofloxacin	>8	>8	4 – >8	0.0 / 95.1	0.0 / 100.0
Moxifloxacin	>8	>8	2 – >8	- / -	- / -
Gatifloxacin	>8	>8	2 – >8	1.0 / 97.1	- / -
Ceftazidime	>16	>16	8 – >16	2.0 / 95.1	- / -
Cefepime	>16	>16	16 – >16	0.0 / 99.0	- / -
Meropenem	>8	>8	1 – >8	10.8 / 87.3	6.9 / 87.3
Piperacillin/tazobactam	>64	>64	>64	0.0 / 100.0	- / -
Amikacin	64	>64	1 – >64	25.5 / 57.8	18.6 / 74.5
Tigecycline[c]	2	4	0.25 – >4	- / -	- / -
Europe (49)					
KPI-10	1	4	0.25 – >8	- / -	- / -
Ciprofloxacin	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Levofloxacin	>8	>8	4 – >8	0.0 / 89.8	0.0 / 100.0
Moxifloxacin	>8	>8	2 – >8	- / -	- / -
Gatifloxacin	8	>8	4 – >8	0.0 / 89.8	- / -
Ceftazidime	>16	>16	16 – >16	0.0 / 98.0	- / -
Cefepime	>16	>16	16 – >16	0.0 / 95.9	- / -
Meropenem	>8	>8	2 – >8	8.2 / 83.7	4.1 / 83.7
Piperacillin/tazobactam	>64	>64	>64	0.0 / 100.0	- / -
Amikacin	>64	>64	1 – >64	30.6 / 61.2	30.6 / 69.4
Tigecycline[c]	1	2	0.25 – 4	- / -	- / -
Latin America (32)					
KPI-10	1	2	0.25 – 4	- / -	- / -
Ciprofloxacin	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Levofloxacin	>8	>8	4 – >8	0.0 / 90.6	0.0 / 100.0
Moxifloxacin	8	>8	2 – >8	- / -	- / -
Gatifloxacin	8	>8	2 – >8	6.3 / 78.1	- / -
Ceftazidime	>16	>16	16 – >16	0.0 / 90.6	- / -
Cefepime	>16	>16	16 – >16	0.0 / 96.9	- / -
Meropenem	>8	>8	1 – >8	18.8 / 81.3	15.6 / 81.3
Piperacillin/tazobactam	>64	>64	64 – >64	3.1 / 96.9	- / -
Amikacin	>64	>64	2 – >64	18.8 / 71.9	18.8 / 81.3
Tigecycline[c]	0.5	2	0.06 – >4	- / -	- / -
Asia-Pacific (30)					
KPI-10	1	2	0.25 – 8	- / -	- / -
Ciprofloxacin	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Levofloxacin	8	>8	4 – >8	0.0 / 86.7	0.0 / 100.0
Moxifloxacin	>8	>8	4 – >8	- / -	- / -
Gatifloxacin	8	>8	4 – >8	0.0 / 86.7	- / -
Ceftazidime	>16	>16	16 – >16	0.0 / 96.7	- / -
Cefepime	>16	>16	>16	0.0 / 100.0	- / -
Meropenem	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Piperacillin/tazobactam	>64	>64	>64	0.0 / 100.0	- / -
Amikacin	>64	>64	2 – >64	20.0 / 76.7	16.7 / 80.0
Tigecycline[c]	1	1	0.25 – 2	- / -	- / -

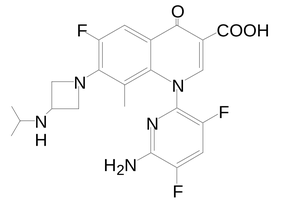
a. Includes: *Acinetobacter baumannii* (198 strains), and unspeciated *Acinetobacter* (15 strains).
b. Criteria as published by the CLSI [2012] and EUCAST [2012].
c. USA-FDA breakpoints were applied [Tygacil Product Insert, 2012].

Table 3. Activity of KPI-10 and comparator antimicrobial agents when tested against 65 isolates of OXA-producing *Acinetobacter* spp.[a] (all regions).

Organism/ antimicrobial agent (no. tested)	MIC (µg/ml) MIC_{50}	MIC_{90}	Range	CLSI[b] %S / %R	EUCAST[b] %S / %R
OXA+ *Acinetobacter* spp. (65, **All regions**)[a]					
KPI-10	1	2	0.015 – 8	- / -	- / -
Ciprofloxacin	>8	>8	0.06 – >8	3.1 / 96.9	3.1 / 96.9
Levofloxacin	>8	>8	0.06 – >8	3.1 / 93.8	3.1 / 96.9
Moxifloxacin	>8	>8	0.03 – >8	- / -	- / -
Gatifloxacin	8	>8	≤0.06 – >8	6.2 / 83.1	- / -
Ceftazidime	>16	>16	2 – >16	3.1 / 93.8	- / -
Cefepime	>16	>16	16 – >16	0.0 / 93.8	- / -
Meropenem	>8	>8	4 – >8	3.1 / 90.8	0.0 / 90.8
Piperacillin/tazobactam	>64	>64	>64	0.0 / 100.0	- / -
Amikacin	>64	>64	2 – >64	15.4 / 73.8	9.2 / 84.6
Tigecycline[c]	1	2	0.12 – >4	- / -	- / -
North America (11)					
KPI-10	1	2	0.25 – 2	- / -	- / -
Ciprofloxacin	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Levofloxacin	>8	>8	4 – >8	0.0 / 90.9	0.0 / 100.0
Moxifloxacin	>8	>8	1 – >8	- / -	- / -
Gatifloxacin	>8	>8	2 – >8	9.1 / 90.9	- / -
Ceftazidime	>16	>16	2 – >16	9.1 / 81.8	- / -
Cefepime	>16	>16	16 – >16	0.0 / 90.9	- / -
Meropenem	>8	>8	8 – >8	0.0 / 90.9	0.0 / 90.9
Piperacillin/tazobactam	>64	>64	>64	0.0 / 100.0	- / -
Amikacin	64	>64	4 – >64	9.1 / 63.6	9.1 / 90.9
Tigecycline[c]	2	2	0.25 – 4	- / -	- / -
Europe (31)					
KPI-10	1	2	0.015 – 8	- / -	- / -
Ciprofloxacin	>8	>8	0.06 – >8	6.5 / 93.5	6.5 / 93.5
Levofloxacin	>8	>8	0.06 – >8	6.5 / 90.3	6.5 / 93.5
Moxifloxacin	>8	>8	0.03 – >8	- / -	- / -
Gatifloxacin	8	>8	≤0.06 – >8	9.7 / 80.6	- / -
Ceftazidime	>16	>16	8 – >16	3.2 / 93.5	- / -
Cefepime	>16	>16	16 – >16	0.0 / 93.5	- / -
Meropenem	>8	>8	4 – >8	6.5 / 87.1	0.0 / 87.1
Piperacillin/tazobactam	>64	>64	>64	0.0 / 100.0	- / -
Amikacin	>64	>64	2 – >64	29.0 / 58.1	16.1 / 71.0
Tigecycline[c]	1	2	0.12 – >4	- / -	- / -
Latin America (23)					
KPI-10	1	2	0.5 – 8	- / -	- / -
Ciprofloxacin	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Levofloxacin	8	>8	8 – >8	0.0 / 100.0	0.0 / 100.0
Moxifloxacin	8	>8	4 – >8	- / -	- / -
Gatifloxacin	8	>8	4 – >8	0.0 / 82.6	- / -
Ceftazidime	>16	>16	>16	0.0 / 100.0	- / -
Cefepime	>16	>16	16 – >16	0.0 / 95.7	- / -
Meropenem	>8	>8	8 – >8	0.0 / 95.7	0.0 / 95.7
Piperacillin/tazobactam	>64	>64	>64	0.0 / 100.0	- / -
Amikacin	>64	>64	64 – >64	0.0 / 100.0	0.0 / 100.0
Tigecycline[c]	1	2	0.25 – 4	- / -	- / -

a. Includes: *Acinetobacter baumannii* (63 strains), *A. calcoaceticus* (1 strain), and unspeciated *Acinetobacter* (1 strain).
b. Criteria as published by the CLSI [2012] and EUCAST [2012].
c. USA-FDA breakpoints were applied [Tygacil Product Insert, 2012].

Figure 1. Chemical structure of KPI-10 (WQ-3810)



Conclusions

- KPI-10 demonstrated potent activity against MDR-*Acinetobacter* spp. and against OXA-producing *Acinetobacter* spp.
- It was the only fluoroquinolone with sufficient potency to exhibit an on-scale MIC_{90} value of 2 µg/ml; the MIC_{90} values for other fluoroquinolones were at >8 µg/ml. Susceptibility rates for other fluoroquinolones, ceftazidime, cefepime, meropenem, piperacillin-tazobactam were <10.0%; amikacin susceptibility was 24.9%.
- KPI-10 merits further evaluation for its potential to address serious hospital infections where MDR *Acinetobacter* spp. may be a concern.

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