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JNJ-Q2: a New Fluoroquinolone with Potent in Vitro Activity against *Staphylococcus aureus*, including Methicillin- and Fluoroquinolone-resistant Strains

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AMENDED ABSTRACT

Background: JNJ-Q2 is a broad-spectrum bactericidal fluoroquinolone (FQ) with potent activity against Gram-positive pathogens including methicillin-resistant (MR) *S. aureus* (SA) and Gram-negative pathogens, and is in early clinical development for the treatment of acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia. In this study, the in vitro activity of JNJ-Q2 and FQ comparators was evaluated against selected *S. aureus* isolated in 2008-2009 from patients with ABSSSI in the United States (USA).

Methods: A total of 511 SA were selected for FQ and MR status as described in the Table. Isolates were tested against JNJ-Q2, moxifloxacin, levofloxacin and ciprofloxacin as per the CLSI broth microdilution method (M07-A8; M100-S20).

Results: JNJ-Q2 MIC was highly active (MIC_{90}, <=0.008-0.015 µg/ml) against all FQ-susceptible (S)-SA tested, independent of methicillin resistance (R) status. JNJ-Q2 was also very active (MIC_{90}, 0.5-1 µg/ml) against most FQR-SA tested, independent of MR status, but the activity was lower than that observed for the FQS population. Overall, 87% of all FQR-MRSA isolates were inhibited by JNJ-Q2 at an MIC of <=0.5 µg/ml. JNJ-Q2 was the most potent fluoroquinolone tested overall and against all subgroups when compared directly to moxifloxacin, levofloxacin, and ciprofloxacin.

Conclusions: JNJ-Q2 demonstrated very potent activity against this collection of *S. aureus*, including MR and FQR strains, isolated from patients with ABSSSI in USA hospitals during 2008-2009. JNJ-Q2 activities were many folds greater than the three comparator FQ's against all SA subgroups. The JNJ-Q2 in vitro results are very promising and support clinical development of this new FQ for treatment of ABSSSI.

INTRODUCTION

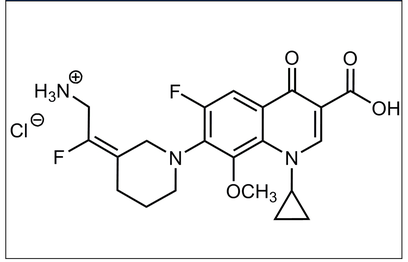
The quinolone class of antimicrobial agents have demonstrated high clinical utility in a variety of human infections and have become one of the most widely used classes. Resistance to fluoroquinolones (FQ) usually occurs by alterations to target enzymes (DNA gyrase and topoisomerase IV) but also by efflux and/or decreased uptake.

For *Staphylococcus aureus*, current (2008) surveillance data reports an overall global FQ resistance rate of ~30%. In 2008 in the United States (USA), although FQ resistance was only 11% in methicillin-susceptible *S. aureus* (MSSA), it was >70% in methicillin-resistant (MRSA) isolates with the overall prevalence of MRSA being >55%.

JNJ-Q2 (Figure 1) is a novel fluorinated 4-quinolone with potent activity against Gram-positive pathogens (including MRSA) and Gram-negative pathogens and it is in clinical development for the treatment of acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP).

In this presentation, we summarize *in vitro* testing results for JNJ-Q2 and FQ comparators against selected *S. aureus* isolated in 2008-2009 from patients with ABSSSI in the USA.

Figure 1. Chemical structure of JNJ-Q2.



MATERIALS AND METHODS

Bacterial Strain Collection. The SENTRY Antimicrobial Surveillance Program has monitored a worldwide collection of pathogens since 1997, and the 2008-2009 samples were examined to select representative strains of JNJ-Q2-targeted pathogens from the USA and from patients with ABSSSI. Species identifications were performed by the submitting laboratories with confirmation performed by the central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA).

Susceptibility Test Methods. All isolates were tested for susceptibility by reference broth microdilution methods using the Clinical and Laboratory Standards Institute recommendations (CLSI; M07-A8, 2009). Susceptibility testing was performed by using validated broth microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, Ohio, USA). Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S20-U, 2010) quality control (QC) strains, including *S. aureus* ATCC 29213. Categorical interpretation of comparator MIC values was performed according to CLSI (M100-S20-U, 2010) criteria, when available.

RESULTS

- Against all *S. aureus* (511 isolates) tested, JNJ-Q2 was very active with a MIC_{50}, MIC_{90}, and MIC range of 0.12, 0.5, and ≤0.008 to 4 µg/ml, respectively (Table 1). Comparing MIC_{50} values, JNJ-Q2 demonstrated 16-, 64- and 128- fold greater activity than moxifloxacin, levofloxacin, and ciprofloxacin, respectively (Table 1).
- In this selected population, antimicrobial resistance was elevated for levofloxacin and ciprofloxacin (both 80.0%), moxifloxacin (78.1%), and erythromycin (83.8%). Clindamycin showed a moderate rate of resistance (28.8%). In contrast, resistance was very low for tetracycline (4.5%) and trimethoprim/sulfamethoxazole (1.8%). All isolates were susceptible to vancomycin, linezolid, and daptomycin (Table 2).
- When testing the 308 FQR-MRSA, JNJ-Q2 was still many-fold more active than the comparator fluoroquinolone antimicrobial agents (Tables 1 and 2). Overall, 86.7% of all FQR-MRSA isolates were inhibited by JNJ-Q2 at an MIC of ≤0.5 µg/ml. However, the MIC_{50} (0.25 µg/ml) and MIC_{90} (1 µg/ml) values were the highest in this subgroup compared to the other 3 subgroups and the overall collection. In addition, 13/14 isolates with MIC values >1 µg/ml (13 isolates at 2 µg/ml and one isolate at 4 µg/ml) were in the FQR-MRSA subgroup, with the remaining isolate also being fluoroquinolone-resistant (in the FQR-MSSA subgroup).
- Against the FQR-MSSA subgroup (Tables 1 and 2), JNJ-Q2, moxifloxacin, levofloxacin, and ciprofloxacin all had similar activity or only two-fold lower than that observed in the FQR-MRSA subgroup.
- JNJ-Q2 was most active against fluoroquinolone-susceptible isolates, regardless of MRSA or MSSA status. The MIC_{50} and MIC_{90} for FQS-MRSA and FQS-MSSA (Tables 1 and 2) were at ≤0.008 µg/ml and ≤0.008-0.015 µg/ml, respectively. The highest MIC observed in both groups of organisms was only 0.015 µg/ml.

Table 1. MIC and cumulative percent inhibited distribution of JNJ-Q2 and comparison fluoroquinolones against each *S. aureus* subgroup

Subgroup (no. tested) /antimicrobial[a]	No. (cumulative %) of isolates inhibited at antimicrobial MIC (µg/ml):													MIC_{50}	MIC_{90}
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16		
All isolates (511)															
JNJ-Q2	90 (17.6)	12 (20.0)	0 (20.0)	0 (20.0)	170 (53.2)	161 (84.7)	30 (90.6)	34 (97.3)	13 (99.8)	1 (100.0)				0.12	0.5
Moxifloxacin			27 (5.3)	70 (19.0)	5 (20.0)	0 (20.0)	0 (20.0)	10 (21.9)	179 (57.0)	62 (69.1)	94 (87.5)	10 (89.4)	54 (100.0)	2	>16
Levofloxacin					12 (2.3)	86 (19.2)	4 (20.0)	0 (20.0)	0 (20.0)	120 (43.4)	75 (58.1)	53 (68.5)	161 (100.0)	8	>16
Ciprofloxacin					1 (0.2)	22 (4.5)	75 (19.2)	4 (20.0)	0 (20.0)	0 (20.0)	94 (38.4)	88 (55.6)	227 (100.0)	16	>16
FQR-MRSA (308)															
JNJ-Q2					127 (41.2)	116 (78.9)	24 (86.7)	28 (95.8)	12 (99.7)	1 (100.0)				0.25	1
Moxifloxacin								7 (2.3)	131 (44.8)	46 (59.7)	69 (82.1)	9 (85.1)	46 (100.0)	4	>16
Levofloxacin										92 (29.9)	51 (46.4)	36 (58.1)	129 (100.0)	16	>16
Ciprofloxacin											74 (24.0)	62 (44.2)	172 (100.0)	>16	>16
FQR-MSSA (101)															
JNJ-Q2					43 (42.6)	45 (87.1)	6 (93.1)	6 (99.0)	1 (100.0)					0.25	0.5
Moxifloxacin								3 (3.0)	48 (50.5)	16 (66.3)	25 (91.1)	1 (92.1)	8 (100.0)	2	>16
Levofloxacin										28 (27.7)	24 (51.5)	17 (68.3)	32 (100.0)	8	>16
Ciprofloxacin											20 (19.8)	26 (45.5)	55 (100.0)	>16	>16
FQS-MRSA (50)															
JNJ-Q2	49 (98.0)	1 (100.0)												≤0.008	≤0.008
Moxifloxacin			13 (26.0)	36 (98.0)	1 (100.0)									0.06	0.06
Levofloxacin					2 (4.0)	46 (96.0)	2 (100.0)							0.25	0.25
Ciprofloxacin						7 (14.0)	41 (96.0)	2 (100.0)						0.5	0.5
FQS-MSSA (52)															
JNJ-Q2	41 (78.9)	11 (100.0)												≤0.008	0.015
Moxifloxacin			14 (26.9)	34 (92.3)	4 (100.0)									0.06	0.06
Levofloxacin					10 (19.2)	40 (96.2)	2 (100.0)							0.25	0.25
Ciprofloxacin					1 (1.9)	15 (30.8)	34 (96.2)	2 (100.0)						0.5	0.5

a. FQ = fluoroquinolone, S = susceptible, R = resistant, MSSA = methicillin-susceptible *S. aureus*, MRSA = methicillin-susceptible *S. aureus*.

Table 2. Antimicrobial activity of JNJ-Q2 and comparator antimicrobials against 511 *S. aureus* by fluoroquinolone- and methicillin- resistance status

Organism (no. tested)/ Antimicrobial agent[a]	MIC in µg/ml			CLSI[b] %S / %R	EUCAST[b] %S / %R
	MIC_{50}	MIC_{90}	Range		
All isolates (511)					
JNJ-Q2	0.12	0.5	≤0.008 – 4	-/- / - -	- / -
Levofloxacin	8	>16	0.12 – >16	20.0 / 80.0	20.0 / 80.0
Moxifloxacin	2	>16	0.03 – >16	20.0 / 78.1	20.0 / 78.1
Ciprofloxacin	16	>16	0.12 – >16	20.0 / 80.0	20.0 / 80.0
Oxacillin	>2	>2	≤0.25 – >2	29.9 / 70.1	29.9 / 70.1
Penicillin	32	>32	≤0.015 – >32	10.0 / 90.0	10.0 / 90.0
Erythromycin	>2	>2	≤0.25 – >2	16.0 / 83.8	16.0 / 83.8
Clindamycin	≤0.25	>2	≤0.25 – >2	70.8 / 28.8	70.6 / 29.2
Linezolid	2	2	0.5 – 4	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – >8	94.9 / 4.5	93.5 / 6.5
Trim/sulfa[d]	≤0.5	≤0.5	≤0.5 – >2	98.2 / 1.8	98.2 / 1.8
Daptomycin	0.5	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
FQR-MRSA (308)					
JNJ-Q2	0.25	1	0.12 – 4	- / -	- / -
Levofloxacin	16	>16	4 – >16	0.0 / 100.0	0.0 / 100.0
Moxifloxacin	4	>16	1 – >16	0.0 / 97.7	0.0 / 97.7
Ciprofloxacin	>16	>16	8 – >16	0.0 / 100.0	0.0 / 100.0
Erythromycin	>2	>2	≤0.25 – >2	6.5 / 93.5	6.5 / 93.5
Clindamycin	≤0.25	>2	≤0.25 – >2	61.7 / 38.0	61.4 / 38.3
Linezolid	2	2	0.5 – 4	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – >8	95.8 / 3.6	93.5 / 6.5
Trim/sulfa[d]	≤0.5	≤0.5	≤0.5 – >2	98.1 / 1.9	98.1 / 1.9
Daptomycin	0.5	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
FQR-MSSA (101)					
JNJ-Q2	0.25	0.5	0.12 – 2	- / -	- / -
Levofloxacin	8	>16	4 – >16	0.0 / 100.0	0.0 / 100.0
Moxifloxacin	2	8	1 – >16	0.0 / 97.0	0.0 / 97.0
Ciprofloxacin	>16	>16	8 – >16	0.0 / 100.0	0.0 / 100.0
Erythromycin	>2	>2	≤0.25 – >2	15.8 / 84.2	15.8 / 84.2
Clindamycin	≤0.25	>2	≤0.25 – >2	71.3 / 28.7	71.3 / 28.7
Linezolid	2	2	1 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – >8	96.0 / 4.0	96.0 / 4.0
Trim/sulfa[d]	≤0.5	≤0.5	≤0.5 – >2	97.0 / 3.0	97.0 / 3.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
FQS-MRSA (50)					
JNJ-Q2	≤0.008	≤0.008	≤0.008 – 0.015	- / -	- / -
Levofloxacin	0.25	0.25	0.12 – 0.5	100.0 / 0.0	100.0 / 0.0
Moxifloxacin	0.06	0.06	0.03 – 0.12	100.0 / 0.0	100.0 / 0.0
Ciprofloxacin	0.5	0.5	0.25 – 1	100.0 / 0.0	100.0 / 0.0
Erythromycin	>2	>2	≤0.25 – >2	6.0 / 92.0	6.0 / 92.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	98.0 / 2.0	98.0 / 2.0
Linezolid	2	2	1 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – >8	92.0 / 6.0	92.0 / 8.0
Trim/sulfa[d]	≤0.5	≤0.5	≤0.5	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.5	0.5	0.25 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.5 – 1	100.0 / 0.0	100.0 / 0.0
FQS-MSSA (52)					
JNJ-Q2	≤0.008	0.015	≤0.008 – 0.015	- / -	- / -
Levofloxacin	0.25	0.25	0.12 – 0.5	100.0 / 0.0	100.0 / 0.0
Moxifloxacin	0.06	0.06	0.03 – 0.12	100.0 / 0.0	100.0 / 0.0
Ciprofloxacin	0.5	0.5	0.12 – 1	100.0 / 0.0	100.0 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	82.7 / 17.3	82.7 / 17.3
Clindamycin	≤0.25	≤0.25	≤0.25 – 1	98.1 / 0.0	98.1 / 1.9
Linezolid	2	2	1 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – >8	90.4 / 9.6	90.4 / 9.6
Trim/sulfa[d]	≤0.5	≤0.5	≤0.5 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.5	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0

a. FQ = fluoroquinolone, S = susceptible, R = resistant, MSSA = methicillin-susceptible *S. aureus*, MRSA = methicillin-susceptible *S. aureus*.
b. Criteria as published by the CLSI [2010] and EUCAST [2010].
c. - = No breakpoint has been established.
d. Trimethoprim/sulfamethoxazole.

CONCLUSIONS

- JNJ-Q2 was highly potent (MIC_{90}, ≤0.008-0.015 µg/ml) against all FQS-*S. aureus* tested, a potency independent of methicillin susceptibility patterns.
- JNJ-Q2 was very active (MIC_{90}, 0.5-1 µg/ml) against most FQR-SA tested, independent of methicillin resistance status, but the potency was lower than that seen among the FQS population (≥32-fold at the MIC_{50} level).
- JNJ-Q2 was the most potent fluoroquinolone class agent tested overall and against all *S. aureus* subgroups when compared directly to moxifloxacin, levofloxacin, and ciprofloxacin.

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