Activity of JNJ-Q2, a New Fluoroquinolone, Tested Against Contemporary (2011) Acute Bacterial Skin and Skin-Structure Infection Pathogens from Europe

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Abstract

Objectives: To determine the activity of JNJ-Q2 tested against contemporary (2011) European isolates of the most common bacterial species isolated from patients with acute bacterial skin and skin-structure infections (ABSSSI). JNJ-Q2 is a broad-spectrum bactericidal fluoroquinolone (FQ) with potent activity against Gram-positive and -negative pathogens, including methicillin-resistant (MR) *Staphylococcus aureus* (SA), and is in clinical development for the treatment of ABSSSI and community-acquired bacterial pneumonia.

Methods: A total of 1,613 pathogens were collected from patients in 24 medical centers in 11 European countries (including Turkey and Israel) in 2011. Species/organism group (number of isolates tested) were: SA (1,416) and beta-haemolytic streptococci (βHS, 197; 33.5% *S. pyogenes*). Isolates were tested for susceptibility by CLSI broth microdilution methods (M07-A9 and M100-S22). Susceptibility interpretations for comparator agents were determined using EUCAST (2012) and CLSI breakpoints.

Results: Table 1 shows the cumulative percentage MIC frequency against the four species/groups tested. Against 1,416 SA, JNJ-Q2 ($MIC_{50/90}$, 0.008/0.25 mg/L) inhibited all isolates at a MIC ≤2 mg/L. Although activity was lower against MRSA (MIC_{50}, 0.25 mg/L) compared to methicillin-susceptible (MS) SA (MIC_{50}, 0.008 mg/L), 98.2% of MRSA were inhibited at a JNJ-Q2 MIC value of ≤0.5 mg/L. Against MRSA, JNJ-Q2 was eight- to at least 32-fold more active than moxifloxacin (MOX; $MIC_{50/90}$, 2/≥8 mg/L) and at least 32-fold more active than levofloxacin (LEV; $MIC_{50/90}$, ≥8/≥8 mg/L) and ciprofloxacin (CIP; $MIC_{50/90}$, ≥8/≥8 mg/L). JNJ-Q2 demonstrated excellent activity ($MIC_{50/90}$, 0.015/0.015 mg/L) against βHS, inhibiting 100.0% of isolates at a MIC of ≤0.12 mg/L. Using MIC_{90} results, JNJ-Q2 was 16-fold more active than MOX ($MIC_{50/90}$, ≤0.12/0.25 mg/L) and 64-fold more active than CIP ($MIC_{50/90}$, 0.5/1 mg/L) against βHS.

Conclusions: JNJ-Q2 demonstrated very potent activity against this collection of common ABSSSI pathogens isolated from patients in European medical centers during 2011. JNJ-Q2 exhibited eight-fold or greater activity compared to CIP, LEV and MOX against these isolates. The JNJ-Q2 *in vitro* results remain very promising and support further clinical development of this new FQ for treatment of ABSSSI, including cases caused by MRSA.

Introduction

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

JNJ-Q2 is a novel fluorinated 4-quinolone with demonstrated potent activity against Gram-positive pathogens (including MRSA) and Gram-negative pathogens. It is in clinical development for the treatment of acute bacterial skin and skin-structure infection (ABSSSI), and has been shown to have balanced potency against both DNA gyrase and topoisomerase IV.

In this presentation, we summarize *in vitro* test results for JNJ-Q2 and comparator antimicrobial agents tested against contemporary (2011) Gram-positive pathogens isolated from patients with ABSSSI in Europe.

Materials and Methods

Bacterial Strain Collection. The SENTRY Antimicrobial Surveillance Program has monitored a worldwide collection of pathogens each year since 1997, and the 2011 samples were examined to select JNJ-Q2-targeted pathogens from European patients with ABSSSI. A total of 1,613 organisms were collected from patients with ABSSSI in 24 medical centers in 11 European countries (including Turkey and Israel). Species identifications were performed by the submitting laboratories with confirmation performed by the central reference 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-A9, 2012) in validated panels manufactured by ThermoFisher Scientific Inc, formerly TREK Diagnostics Systems (Cleveland, Ohio, USA). The quality assurance of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S22, 2012) control strains, including *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619. Categorical interpretation of comparator MIC values was performed according to CLSI (M100-S22, 2012) and EUCAST (2012) criteria.

Results

- Against all *S. aureus* (1,416 isolates from European sites) tested, JNJ-Q2 was very active with a MIC_{50}, MIC_{90}, and MIC range of 0.008, 0.25, and ≤0.002 to 2 mg/L, respectively (Table 1). Comparing MIC_{90} values, JNJ-Q2 demonstrated 16-fold greater activity than moxifloxacin and at least 32-fold greater activity than both ciprofloxacin and levofloxacin (Table 2).
- By EUCAST interpretive criteria (2012), antimicrobial resistance in *S. aureus* was elevated for levofloxacin (27.8%), ciprofloxacin (29.7%), moxifloxacin (21.7%), and erythromycin (29.0%). In contrast, resistance was lower for clindamycin (8.2%), tetracycline (5.9%) and trimethoprim/sulfamethoxazole (0.6%). All isolates were susceptible to vancomycin, daptomycin and linezolid (Table 2).
- JNJ-Q2 was the most active agent tested against 1,032 MSSA. The MIC_{50} and MIC_{90} were at 0.008 mg/L and 0.015 mg/L, respectively, with 100.0% of isolates inhibited at a MIC of ≤1 mg/L.
- When testing the 384 MRSA (27.1% of total), JNJ-Q2 was many-fold more potent than the comparator fluoroquinolone agents with 98.2 and 100.0% of isolates inhibited at MIC values of 0.5 and 2 mg/L, respectively (Table 1). However, due to much higher rates of fluoroquinolone resistance (72.4 to 91.4% by EUCAST interpretations) in the MRSA subpopulation, the MIC_{50} (0.25 mg/L) and MIC_{90} (0.5 mg/L) values were higher compared to MSSA (Table 2).
- Against 197 β-haemolytic streptococci (including 66 [33.5%] *S. pyogenes*), JNJ-Q2 was the most potent (MIC_{90}, 0.015 mg/L) fluoroquinolone agent tested with all isolates being inhibited at an MIC of ≤0.12 mg/L. JNJ-Q2 demonstrated many-fold higher activity than levofloxacin, moxifloxacin and ciprofloxacin (Table 2).

Table 2. Antimicrobial activity of JNJ-Q2 and comparator antimicrobials tested against 1,613 ABSSSI pathogens isolated in Europe (2011).

Organism (no. tested)/ Antimicrobial agent[a]	MIC in mg/L: MIC_{50}	MIC_{90}	Range	CLSI[b] %S / %R	EUCAST[b] %S / %R
All *S. aureus* (1,416)					
JNJ-Q2	0.008	0.25	≤0.002 – 2	-[c] / -	- / -
Levofloxacin	0.25	>4	≤0.12 – >4	71.4 / 27.8	71.4 / 27.8
Moxifloxacin	≤0.12	4	≤0.12 – >4	72.2 / 21.7	72.2 / 21.7
Ciprofloxacin	0.25	>4	≤0.03 – >4	70.3 / 28.6	70.3 / 29.7
Oxacillin	0.5	>2	≤0.25 – >2	72.9 / 27.1	72.9 / 27.1
Erythromycin	0.25	>16	≤0.12 – >16	70.1 / 27.5	70.3 / 29.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	91.8 / 8.1	91.2 / 8.2
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	0.5	≤0.25 – >8	94.4 / 5.1	93.9 / 5.9
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	99.4 / 0.6	99.4 / 0.6
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
MRSA (384)					
JNJ-Q2	0.25	0.5	≤0.002 – 2	- / -	- / -
Levofloxacin	>4	>4	≤0.12 – >4	9.1 / 90.6	9.1 / 90.6
Moxifloxacin	2	>4	≤0.12 – >4	11.5 / 72.4	11.5 / 72.4
Ciprofloxacin	>4	>4	0.12 – >4	8.3 / 91.4	8.6 / 91.4
Erythromycin	>16	>16	≤0.12 – >16	32.5 / 63.3	33.1 / 65.1
Clindamycin	≤0.25	>2	≤0.25 – >2	75.8 / 24.2	75.0 / 24.2
Linezolid	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	4	≤0.25 – >8	90.1 / 9.1	89.6 / 10.2
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	98.4 / 1.6	98.4 / 1.3
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.2
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
MSSA (1,032)					
JNJ-Q2	0.008	0.015	≤0.002 – 1	- / -	- / -
Levofloxacin	≤0.12	0.25	≤0.12 – >4	94.2 / 5.5	94.2 / 5.5
Moxifloxacin	≤0.12	≤0.12	≤0.12 – >4	94.8 / 2.8	94.8 / 2.8
Ciprofloxacin	0.25	0.5	≤0.12 – >4	90.2 / 6.7	93.3 / 6.7
Erythromycin	0.5	>16	≤0.12 – >16	84.0 / 14.2	84.1 / 15.5
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	96.0 / 3.6	97.3 / 2.2
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Tetracycline	≤0.25	≤0.25	≤0.25 – >8	96.0 / 3.6	95.4 / 4.4
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	99.7 / 0.3	99.7 / 0.3
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
β-haemolytic streptococci (197)					
JNJ-Q2	0.015	0.015	≤0.002 – 0.12	- / -	- / -
Levofloxacin	0.5	1	≤0.12 – >4	99.0 / 1.0	95.4 / 1.0
Moxifloxacin	≤0.12	0.25	≤0.12 – 4	- / -	99.0 / 1.0
Ciprofloxacin	0.5	1	≤0.03 – >4	- / -	- / -
Penicillin	≤0.06	≤0.06	≤0.06	100.0 / -	100.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	≤1	- / -	100.0 / 0.0
Erythromycin	≤0.12	4	≤0.12 – >16	78.2 / 21.8	78.2 / 21.8
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	91.4 / 8.6	91.4 / 8.6
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
TMP/SMX[d]	≤0.5	≤0.5	≤0.5 – >4	- / -	97.5 / 2.0
Daptomycin	≤0.06	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0

a. MSSA = methicillin-susceptible *S. aureus*, MRSA = methicillin-resistant *S. aureus*.
b. Criteria as published by the CLSI [2012] and EUCAST [2012].
c. = No breakpoint has been established.
d. Trimethoprim/sulfamethoxazole.

Conclusions

- JNJ-Q2 MIC was very active (MIC_{90}, 0.25 mg/L) when tested by reference MIC methods against all *S. aureus* from Europe. JNJ-Q2 was very active (MIC_{90}, 0.5 mg/L) against MRSA, but the potency was slightly lower than that observed among the MSSA population. JNJ-Q2 was the most potent fluoroquinolone class agent tested and against MSSA and MRSA when compared directly to levofloxacin, moxifloxacin and ciprofloxacin.
- JNJ-Q2 was the most potent antimicrobial agent tested (MIC_{90}, 0.015 mg/L) against β-haemolytic streptococci demonstrating many-fold higher activity than levofloxacin, moxifloxacin and ciprofloxacin.
- JNJ-Q2 exhibited very potent activity against this collection of common ABSSSI pathogens isolated from patients in European medical centers during 2011. These encouraging results support the further clinical development of JNJ-Q2 to treat ABSSSI in this region.

Acknowledgment

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Table 1. MIC (mg/L) and cumulative percent inhibited distributions of JNJ-Q2 tested against 1,613 ABSSSI pathogens isolated in European medical centers (2011).

Organism/group (no. tested)	MIC in mg/L (cumulative % inhibited): ≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	MIC_{50}	MIC_{90}
S. aureus (1,416)	434 (30.7)	478 (64.4)	93 (71.0)	7 (71.5)	15 (72.5)	151 (83.2)	196 (97.0)	34 (99.4)	6 (99.9)	2 (100.0)	0.008	0.25
MSSA (1,032)	425 (41.2)	459 (85.7)	85 (93.9)	7 (94.6)	5 (95.1)	31 (98.1)	18 (99.8)	1 (99.9)	1 (100.0)	-	0.008	0.015
MRSA (384)	9 (2.3)	19 (7.3)	8 (9.4)	0 (9.4)	10 (12.0)	120 (43.2)	178 (89.6)	33 (98.2)	5 (99.5)	2 (100.0)	0.25	0.5
βH[a] streptococci (197)	2 (1.0)	62 (32.5)	120 (93.4)	11 (99.0)	1 (99.5)	1 (100.0)	-	-	-	-	0.015	0.015

a. βH=β-haemolytic streptococci including *Streptococcus dysgalactiae* (5 strains), *S. equisimilis* (3 strains), Group A *Streptococcus* (66 strains), Group B *Streptococcus* (74 strains), Group C *Streptococcus* (14 strains), and Group G *Streptococcus* (35 strains).