Activity of JNJ-Q2, a New Fluoroquinolone, Tested Against Contemporary (2010) European Pathogens Isolated from Patients with Community-Acquired Bacterial Pneumonia

1137

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AMENDED ABSTRACT

Objectives: To determine the activity of JNJ-Q2 tested against contemporary (2010) European isolates of the most common bacterial species isolated from patients with community-acquired bacterial pneumonia (CABP). JNJ-Q2 is a broad-spectrum bactericidal fluoroquinolone (FQ) with potent activity against Gram-positive and -negative pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), and is in clinical development for the treatment of CABP and acute bacterial skin and skin structure infection.

Methods: A total of 1,150 respiratory pathogens were collected from patients with CABP in 32 medical centres in 15 countries (including Turkey and Israel). Species (number of isolates tested) were: *Streptococcus pneumoniae* (SPN, 701), *Haemophilus influenzae* (HI, 315), and *Moraxella catarrhalis* (MC, 134). Isolates were tested for susceptibilities by CLSI broth microdilution methods (M07-A8). Susceptibility rates for comparator agents were determined using CLSI and EUCAST breakpoints.

Results: Table 1 shows the cumulative percentage MIC frequency against each species tested. JNJ-Q2 was highly active against all three species inhibiting >98% of all 1,150 isolates at a JNJ-Q2 MIC of ≤0.015 mg/L. Against SPN, resistances to penicillin, azithromycin, ciprofloxacin (CIP), levofloxacin (LEV) and MOX were 5.7, 27.0, 3.1, 0.9 and 0.9%, respectively, with JNJ-Q2 ($MIC_{50/90}$, 0.008/0.015 mg/L) demonstrating 16-fold higher activity compared to MOX ($MIC_{50/90}$, 0.12/0.25 mg/L) and 128-fold higher activity than LEV ($MIC_{50/90}$, 1/1 mg/L) and CIP ($MIC_{50/90}$, 1/2 mg/L). 16.8% of HI were resistant to ampicillin. JNJ-Q2 ($MIC_{50/90}$, ≤0.004/0.015 mg/L) was at least four-fold more active than MOX ($MIC_{50/90}$, 0.015/0.03 mg/L) against HI. JNJ-Q2 ($MIC_{50/90}$, 0.015/0.015 mg/L) was also four-fold more active than MOX ($MIC_{50/90}$, 0.06/0.06 mg/L) against MC.

Conclusions: JNJ-Q2 demonstrated very potent activity against this collection of three common respiratory bacterial pathogens isolated from patients with CABP in European hospitals during 2010, and historically also covers MRSA. JNJ-Q2 also demonstrated four-fold or greater activity compared to CIP, LEV and MOX against all three species, including against strains resistant to these fluoroquinolone antimicrobial agents. These JNJ-Q2 in vitro results are very promising and support clinical development of this new FQ for treatment of CABP.

INTRODUCTION

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

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* test results for JNJ-Q2 and comparator antimicrobial agents against the most common pathogens isolated in 2010 from patients with CABP in Europe.

MATERIALS AND METHODS

Bacterial Strain Collection. The SENTRY Antimicrobial Surveillance Program has monitored a worldwide collection of pathogens since 1997, and the 2010 samples were examined to select a total of 1,150 JNJ-Q2-targeted pathogens from patients with CABP in 32 medical centres in 15 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-A8, 2009) using validated panels manufactured by TREK Diagnostic Systems (Cleveland, Ohio, USA). The quality assurance of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S21, 2011) control strains, including *Streptococcus pneumoniae* ATCC 49619 and *Haemophilus influenzae* ATCC 49247 and 49766. Categorical interpretation of comparator MIC values was performed according to CLSI (M100-S21, 2011) and EUCAST (2011) criteria.

RESULTS

- Against all *S. pneumoniae* (701 isolates) tested, JNJ-Q2 was very active with a MIC_{50}, MIC_{90}, and MIC range of 0.008, 0.015, and ≤0.004 to 1 mg/L, respectively (Table 1). Comparing MIC_{50} values, JNJ-Q2 demonstrated 16-, 128-, and 128-fold greater activity than moxifloxacin (MOX), ciprofloxacin (CIP) and levofloxacin (LEV), respectively (Table 2).
- By EUCAST criteria, antimicrobial resistance (R) in *S. pneumoniae* was elevated for azithromycin (27.0%), clindamycin (18.5%), tetracycline (22.8%), and trimethoprim/sulfamethoxazole (16.8%). Against beta-lactam agents, penicillin R was 5.7% while 77.6 and 81.3% of isolates tested susceptible (S) to cefuroxime and ceftriaxone, respectively. All isolates were S to vancomycin and linezolid with 99.1 % of isolates testing S to both MOX and LEV (Table 2).
- JNJ-Q2 was very active against 315 *H. influenzae* isolates. The MIC_{50} and MIC_{90} for *H. influenzae* were at ≤0.004 mg/L and 0.015 mg/L, respectively, and the highest JNJ-Q2 MIC observed was only 0.12 mg/L. By EUCAST criteria, 16.8% of isolates were ampicillin-R and all isolates were S to MOX and LEV with 99.7% testing S to CIP.
- Against 134 *M. catarrhalis*, JNJ-Q2 (MIC_{90}, 0.015 mg/L) was four-fold more potent than MOX and all isolates were inhibited at a MIC of ≤0.06 mg/L.

Figure 1. Chemical structure of JNJ-Q2

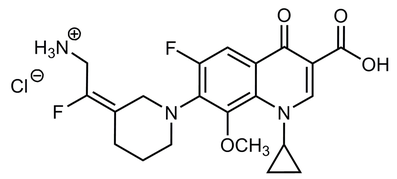

Table 2. Antimicrobial activity of JNJ-Q2 and comparator antimicrobials tested against 1,150 CABP pathogens isolated in Europe (2010)

Organism (no. tested)/ Antimicrobial agent	MIC in mg/L MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[b] %S / %R
S. pneumoniae (701)					
JNJ-Q2	0.008	0.015	≤0.004 – 1	-[b]/ -	- / -
Moxifloxacin	0.12	0.25	0.008 – >8	99.1 / 0.6	99.1 / 0.9
Levofloxacin	1	1	≤0.5 – >4	99.1 / 0.9	99.1 / 0.9
Ciprofloxacin	1	2	0.25 – >4	- / -	0.0 / 3.1
Penicillin[c]	≤0.03	2	≤0.03 – >4	94.3 / 0.1	- / -
Penicillin[d]	≤0.03	2	≤0.03 – >4	71.5 / 17.3	71.5 / 5.7
Amoxicillin/clavulanate	≤1	2	≤1 – 8	93.2 / 3.4	- / -
Ceftriaxone	≤0.06	1	≤0.06 – 4	94.9 / 0.3	81.3 / 0.3
Cefuroxime	≤0.12	4	≤0.12 – 16	78.5 / 20.3	77.6 / 21.5
Tetracycline	0.5	>8	≤0.25 – >8	77.2 / 22.3	76.9 / 22.8
Trim/sulfa[e]	≤0.5	4	≤0.5 – >4	77.3 / 16.8	82.0 / 16.8
Clindamycin	≤0.25	>1	≤0.25 – >1	80.6 / 18.5	81.5 / 18.5
Azithromycin	≤0.25	>4	≤0.25 – >4	73.0 / 26.7	72.3 / 27.0
Linezolid	1	1	≤0.12 – 2	100.0 / -	100.0 / 0.0
Vancomycin	0.25	0.5	≤0.12 – 0.5	100.0 / -	100.0 / 0.0
H. influenzae (315)					
JNJ-Q2	≤0.004	0.015	≤0.004 – 0.12	- / -	- / -
Moxifloxacin	0.015	0.03	≤0.008 – 0.5	100.0 / -	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0 / -	100.0 / 0.0
Ciprofloxacin	≤0.03	≤0.03	≤0.03 – 1	100.0 / -	99.7 / 0.3
Ampicillin	≤1	>8	≤1 – >8	83.2 / 14.9	83.2 / 16.8
Amoxicillin/clavulanate	≤1	2	≤1 – 4	100.0 / 0.0	89.2 / 10.8
Ceftriaxone	≤0.06	≤0.06	≤0.06 – 0.12	100.0 / -	100.0 / 0.0
Cefuroxime	0.5	2	≤0.12 – >16	98.7 / 0.6	76.5 / 5.7
Tetracycline	0.5	1	≤0.25 – >8	98.4 / 1.6	98.1 / 1.6
Trim/sulfa[e]	≤0.5	>4	≤0.5 – >4	73.0 / 23.8	73.0 / 25.7
Azithromycin	1	2	≤0.25 – >4	98.7 / -	0.0 / 1.3
Clarithromycin	8	16	≤0.25 – >32	84.8 / 2.2	0.3 / 1.0
M. catarrhalis (134)					
JNJ-Q2	0.015	0.015	≤0.004 – 0.06	- / -	- / -
Moxifloxacin	0.06	0.06	0.03 – 0.5	- / -	100.0 / 0.0
Levofloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / -	100.0 / 0.0
Ciprofloxacin	≤0.03	≤0.03	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	≤1	100.0 / 0.0	100.0 / 0.0
Ceftriaxone	0.25	0.5	≤0.06 – 2	100.0 / -	99.3 / 0.0
Cefuroxime	1	2	0.25 – 4	100.0 / 0.0	80.6 / 0.7
Tetracycline	≤0.25	0.5	≤0.25 – 1	100.0 / 0.0	100.0 / 0.0
Trim/sulfa[e]	≤0.5	≤0.5	≤0.5 – 4	97.0 / 1.5	97.0 / 2.2
Azithromycin	≤0.25	≤0.25	≤0.25	100.0 / -	100.0 / 0.0
Imipenem	≤0.12	≤0.12	≤0.12	- / -	100.0 / 0.0

a. Criteria as published by the CLSI [2011] and EUCAST [2011].
b. = No breakpoint has been established.
c. Criteria as published by the CLSI [2011] for 'Penicillin parenteral (non-meningitis)'.
d. Criteria as published by the CLSI [2011] for 'Penicillin (oral penicillin V)'.
e. Trimethoprim/sulfamethoxazole.

Table 1. MIC and cumulative percent inhibited distributions of JNJ-Q2 tested against 1,150 CABP pathogens isolated in Europe (2010)

Organism/group	JNJ-Q2 MIC (mg/L) ≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	MIC_{50}	MIC_{90}
S. pneumoniae (701)	26 (3.7)	582 (86.7)	82 (98.4)	2 (98.7)	5 (99.4)	3 (99.9)	0 (99.9)	0 (99.9)	1 (100.0)	0.008	0.015
H. influenzae (315)	192 (61.0)	88 (88.9)	29 (98.1)	4 (99.4)	1 (99.7)	1 (100.0)				≤0.004	0.015
M. catarrhalis (134)	1 (0.8)	51 (38.1)	78 (97.0)	3 (99.3)	1 (100.0)					0.015	0.015

CONCLUSIONS

- JNJ-Q2 MIC was very potent ($MIC_{50/90}$, 0.008/0.015 mg/L) against all *S. pneumoniae* tested and demonstrated 16-, 128-, and 128-fold greater activity than MOX, CIP and LEV, respectively.
- JNJ-Q2 also demonstrated very high activity against *H. influenzae* (MIC_{90}, 0.015 mg/L) and *M. catarrhalis* (MIC_{90}, 0.015 mg/L).
- These promising in vitro results when testing JNJ-Q2, against the three most common causes of CABP isolated in European hospitals, support the further clinical development of this new antimicrobial agent.

ACKNOWLEDGEMENT

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