Amended Abstract

Objective: To determine the activity of JNJ-Q2 against S. aureus isolated from patients with clinically diagnosed acute bacterial skin and skin-structure infection (ABSSSI) in the United States (USA) during a Phase II clinical trial and to evaluate the mechanisms of fluoroquinolone (FQ) resistance (R) in FQ-R strains. JNJ-Q2 is a broad-spectrum bactericidal 4-fluoroquinolone with potent activity against Gram-positive and -negative pathogens.

Methods: During the Phase II clinical trial, a total of 111 baseline S. aureus isolates were obtained from 111 patients, diagnosed with ABSSSI by strict criteria (including 37.8% methicillin-susceptible [MSSA] and 62.2% methicillin-resistant [MRSA]). Susceptibility testing was performed by the CLSI broth microdilution method. Two different quinolone-resistant determinant regions (QRDRs) were amplified by PCR and sequenced for FQ-R strains.

Results: JNJ-Q2 demonstrated good activity against all S. aureus and was very active against both MSSA (MIC ≤0.008/0.12 mg/L) and MRSA (MIC_{\text{MIC50}} 0.12/0.12 mg/L). 51 strains (45.9%) had moxifloxacin MIC values of ≤0.12 mg/L (non-susceptible) and all of these strains carried at least one parC mutation (80Y).

Conclusions: JNJ-Q2 demonstrated very potent activity against contemporary S. aureus isolated from patients in the USA with clinically diagnosed and microbiologically confirmed ABSSSI. JNJ-Q2 exhibited greater activity compared to LEV and MOX, including strains R to currently utilized FQs. These encouraging results support the further clinical development of JNJ-Q2 for ABSSSIs.

Introduction

Quinolone resistance in Staphylococcus aureus results from either mutations in the quinolone-resistance determinant regions (QRDRs) of the target enzymes, commonly DNA gyrase and topoisomerase IV, on the drug efflux, or decreased uptake. JNJ-Q2, a novel fluorinated 4-quinolone, has excellent in vitro activity against both MSSA and MRSA, and is in clinical development for the treatment of acute bacterial skin and skin-structure infection (ABSSSI).

The aims of this study were to determine comparative in vitro activity for JNJ-Q2 tested against S. aureus obtained from a recent (2010) randomized, controlled, double-blind, double-dummy, multicenter Phase II study for JNJ-Q2 compared with linezolid for the treatment of ABSSSI (trial #NCCT1128530).

Materials and Methods

Bacterial Strain Collection. During the Phase II clinical trial, a total of 111 baseline S. aureus isolates were obtained from 111 patients, diagnosed with ABSSSI by strict criteria, in 15 medical centers throughout the United States (USA). Strains were performed by the submitting laboratories with confirmation performed by the central reference laboratory (JMI Laboratories, North Liberty, Iowa, USA). JNJ-Q2 compared with linezolid for the (2010) randomized, controlled, double-blind, double-dummy, multicenter Phase II clinical trial (M100-S22, 2012) efficacy and safety in clinical development for the treatment of ABSSSI (trial #NCT01128530).

S. aureus ATCC 29213 and Enterococcus faecalis ATCC 29212 were used for the quality assurance of the inoculum concentration and growth checks. Culture plates were evaluated for standard: ninth edition. CLSI methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically approved standard: ninth edition. Wayne, PA: CLSI.

Conclusions

In summary, JNJ-Q2 was found to be very active against S. aureus isolated from patients with a defined clinical diagnosis of ABSSSI during a 2010 Phase II clinical trial in the USA, with all 111 baseline strains inhibited at JNJ-Q2 MIC values of ≤0.25 mg/L. JNJ-Q2 was the most potent active compound with activity being many-fold higher than the comparator agents tested.

These favorable results, along with the previously demonstrated low propensity for pathogens to induce rapid mutational resistance to JNJ-Q2, support the further clinical development of JNJ-Q2 to treat ABSSSI, including MRSA.

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References