Solithromycin, a 4th Generation Macrolide and 1st Fluoroketolide, Does Not Prolong the QTc Interval: Results of a Definitive QT Study

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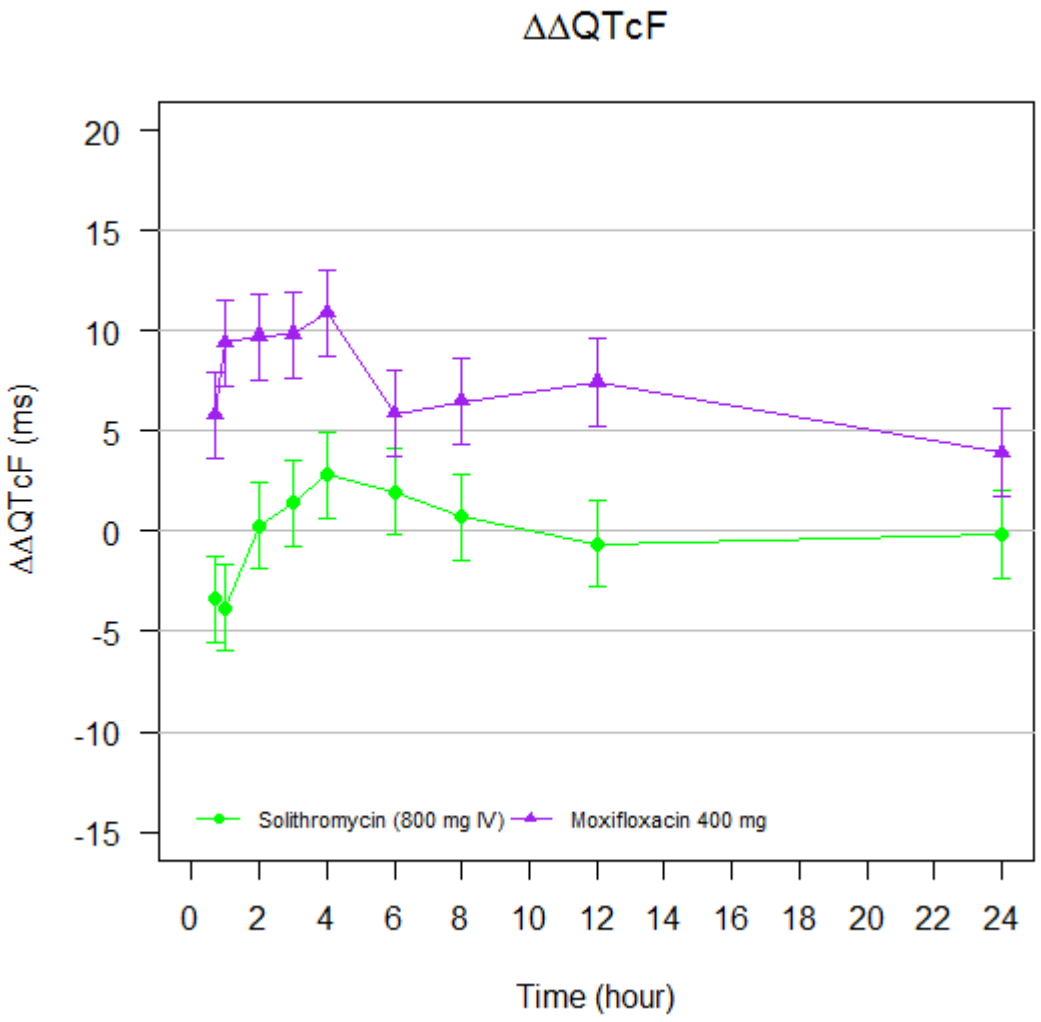
Background: Respiratory quinolone and older macrolide antibiotics have been demonstrated to prolong cardiac repolarization (QTc), with risk of cardiac mortality. Solithromycin, a 4th generation macrolide antibiotic, is under development for treatment of community acquired bacterial pneumonia (CABP).

Methods: This double-blind, randomized thorough QT study, with a 3-way, cross-over design, was conducted in healthy volunteers. Subjects received single dose solithromycin (800 mg IV), 400 mg oral moxifloxacin and placebo infusion in 3 separate treatment periods at 7-day intervals. ECG tracings were extracted from continuous recordings at multiple timepoints. The primary objective was to evaluate the effect of supratherapeutic solithromycin exposure on QTc. The primary endpoint was the baseline-adjusted, placebo-corrected QTcF (ΔΔQTcF); in a linear mixed-effect model of the interval "solithromycin– placebo", if the upper limit of the 2-sided 90% CI fell below 10 ms at all post-dose timepoints, solithromycin would be demonstrated to have no clinically significant QT effect. Single-dose moxifloxacin was administered to determine assay-sensitivity of the trial. Data collection and analyses were conducted in accordance with ICH E14 guidance.

Results: 48 subjects (33 males, 15 females, mean age 36.1 years) were enrolled, 47 completed solithromycin dosing. The geometric mean solithromycin C_{max} was 5.7 µg/mL (mean AUC_{tau} 23,360 ng*hr/mL). Change from baseline QTcF was similar after dosing with solithromycin and placebo, and the resulting ΔΔQTcF was small at all timepoints for solithromycin (Figure). The largest ΔΔQTcF was 2.8 ms with an upper bound of the 90% CI of 4.9 ms. QTc prolongation after moxifloxacin dosing confirmed the study's assay sensitivity with mean ΔΔQTcF of 9.7 to 10.9 ms at the 3 pre-defined timepoints with lower bounds of the 90% CI above 5 ms. In a concentration-effect analysis, a statistically significant, negative slope of solithromycin concentration versus QTcF change was observed (-0.862×10^{-3} ms per ng/mL), supporting the conclusion of the primary by-timepoint analysis. Solithromycin was associated with an increase in mean heart rate of 15 bpm at peak change; this effect on heart rate in healthy subjects was not observed in patients enrolled in a recently completed Phase 3 trial of solithromycin for CABP, in whom mean heart rate declined at all timepoints of evaluation following enrollment. Solithromycin had no effect on cardiac conduction (PR and QRS intervals).

The most frequently reported treatment emergent adverse event (TEAE) following solithromycin was infusion site pain. No serious adverse events and no clinically significant ALT elevations (> 3xULN) were observed.



Conclusions: Unlike older macrolides and ketolides and respiratory quinolone antibiotics, solithromycin does not cause QT prolongation.