Rifampin (RIF) significantly reduces plasma concentrations of fusidic acid (FA) when used in combination for treatment of prosthetic joint infection (PJI)

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Background: FA, an oral antibiotic active against gram-positive bacteria including MRSA, has been in use for decades for treatment of bone and joint infection and more recently with RIF for treatment of PJI. No FA/RIF drug-drug interaction data have been previously reported.

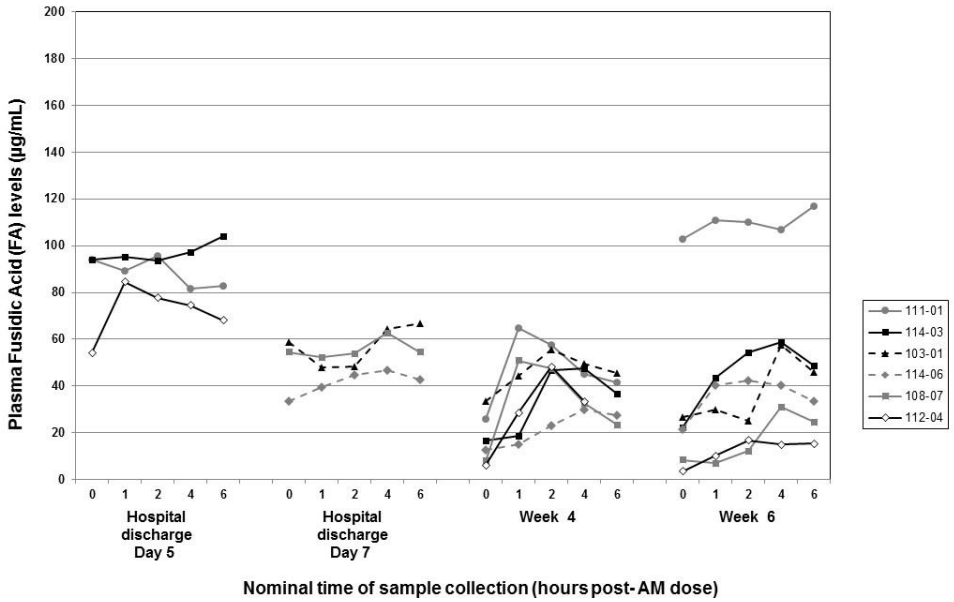
Methods: FA and RIF pharmacokinetics were evaluated in an open-label randomized controlled trial that compared intravenous standard-of-care antibiotic therapy (IV-SOC) with oral FA plus RIF for treatment of hip or knee PJI due to staphylococci (MSSA, MRSA and CoNS) following surgical intervention.

At the time of initial surgery, empiric IV-SOC was initiated. Oral antibiotic therapy was initiated post-operatively while intravenous antibiotics were continued. FA was administered twice daily, with an initial loading dose of 3000 mg (1500 mg BID) followed by a total daily dose (TDD) of 1800 mg (900 mg BID) thereafter, with allowed reduction to 1500 or 1200 mg TDD in case of intolerability. The next day, RIF was added, at a dose of 450 mg BID, with allowed reduction to 300 mg BID for renal insufficiency or intolerability. If oral therapy with FA/RIF was well tolerated and the pathogen(s) susceptible, randomization to complete therapy with either IV SOC or FA/RIF occurred.

At the time of hospital discharge (Day 5-7), Day-14 and Day-28 of oral antibiotic therapy, FA and RIF plasma concentrations were determined.

Results

Study recruitment initiated in December 2012 and the study was closed in July, 2014 following recognition of a significant FA/RIF drug-drug interaction. Seven patients were randomized to continue FA/RIF, and PK profiles for both drugs were obtained for six. Based on prior Phase 1 PK trials with FA dosing alone, FA steady state trough concentrations of 100-200 µg/mL were expected (dependent upon administered dose). In this study, FA levels were substantially lower, and showed progressive decline from Day 5-7 to 14 to 28. In one patient for whom rifampin dosing was discontinued following collection of PK blood samples on Day-14, a substantial rebound of FA levels was observed. These observations suggest that RIF substantially reduces FA exposures (by 50-80%). One patient in this group had treatment failure with isolation of newly RIF (but not FA) - resistant MRSA in follow-up.



Conclusions: Combination therapy with RIF and a second oral antimicrobial agent is recommended therapy for biofilm associated PJI infection. However, when the second agent is FA, a significant drug-drug interaction results in lower FA exposure. This circumstance may create the equivalent of RIF monotherapy and may be associated with emergence of RIF resistance and treatment failure. FA has proven to be a valuable antibiotic for treatment of bone and joint infection, but its use in combination with RIF warrants re-evaluation.

Trial registration: clinicaltrials.gov, NCT01756924.