OVERVIEW OF DRUG DEVELOPMENT CONSIDERATIONS FOR UNCOMPLICATED UROGENITAL GONORRHEA

A TALE OF TWO RECENT TRIALS

Sue K Cammarata, MD
Tunnell Government Services
April 23, 2021
FDA-CDC-NIAID Virtual Public Workshop
Development Considerations of Antimicrobial Drugs for the Treatment of Gonorrhea

TYPICAL ANTIBIOTIC DEVELOPMENT MILESTONES VS GONORRHEA*

Preclinical in vitro data: MICs		Yes, you can do MICs!
Preclinical in vivo data: efficacy in various animal models, thigh model, pneumonia, bacteremia, etc		There has been no clear accepted model
Preclinical PKPD in animal models or in vitro models to estimate dose needed in humans		Without a model, can't work through PKPD assessments
Phase 1 systemic exposure		Yes, you can do!
Phase 1 tissue exposure: lung, urine, blood		?what tissue/fluid levels where? 
Phase 2: dose selection		Risk with small studies
Phase 3 registrational trials		Still risk with regional differences

*Activities focused on dose selection and efficacy

TWO RECENT ANTIBIOTICS WERE STUDIED AGAINST *N. GONORRHOEAE*

BOTH COMPOUNDS HAVE POTENT IN VITRO MICS AND INTRACELLULAR ACCUMULATION

Solithromycin

- Novel macrolide
- Broad spectrum in vitro activity including macrolide-resistant pathogens and azithromycin resistant *N. gonorrhoeae*
  - MIC_{90} 0.25 µg/mL in 218 NG isolates with ~40% azithromycin resistance (Golparian 2012)
- Intracellular activity against internalized gonococci (Mallegol 2013)
- High peak plasma concentrations relative to MICs of N. gonorrhoeae with short systemic exposure

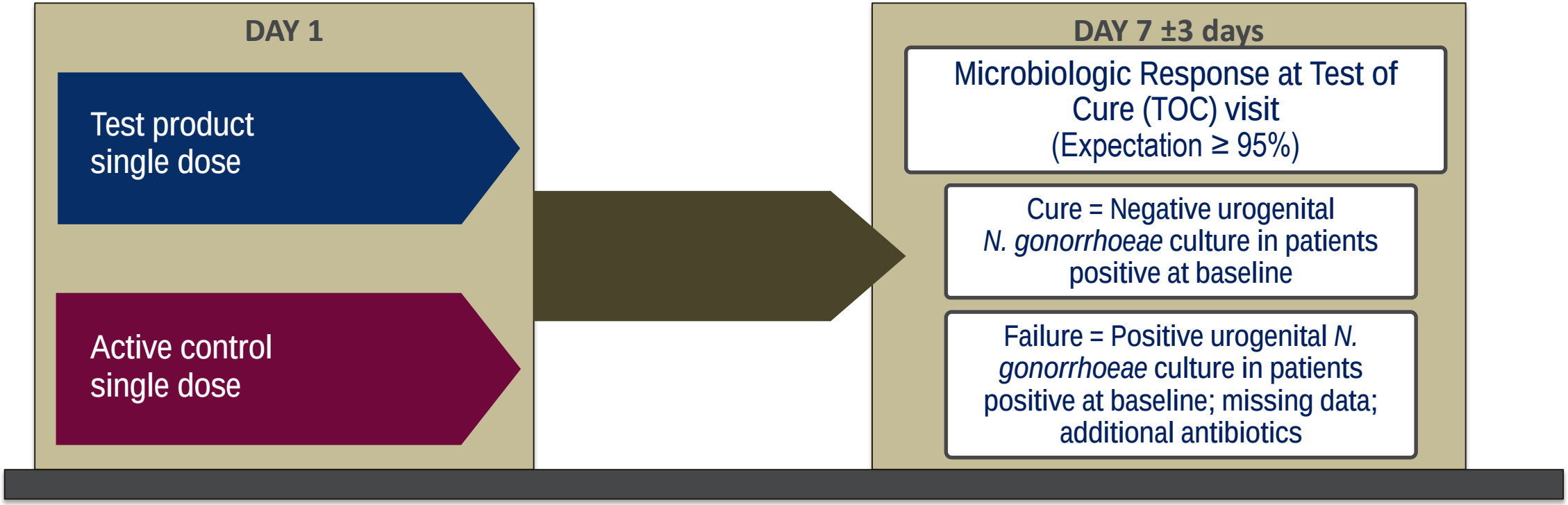
(1200 mg oral: C_{max} = 2 µg/mL ,$T_{1/2}$ ~7 hrs, $AUC_{0-\infty}$ = 27 h•µg/mL; Still 2011)

Delafloxacin

- Anionic fluoroquinolone
- Broad spectrum in vitro activity, including FQ-R *S. aureus* and *N. gonorrhoeae*
  - MIC_{90} 0.125 µg/mL in 110 NG isolates with ~70% ciprofloxacin resistance (Soge 2016)
- In vitro, accumulates intracellularly, which is enhanced at acidic pH (Lemaire 2011)
- Rapid absorption and high systemic peak relative to MICs with relatively short systemic exposure with single dose

(900mg oral: C_{max} = 11.5 µg/mL ,$T_{1/2}$ ~6-8 hrs, $AUC_{0-\infty}$ = 55.2 h•µg/mL; Hoover 2016)

BOTH PRODUCTS HAD SIMILAR PHASE 3 STUDY DESIGNS IN PATIENTS WITH UNCOMPLICATED GONORRHEA (2014-2015)



Solithromycin (Chen, Lancet ID 2019; 19:833-842)

- Solithromycin 1000mg oral
- Active Control: Ceftriaxone 500mg IM/ Azithromycin 1000mg oral
- Randomized 1:1; Open Label; non-inferiority (10%)
- Had prior successful phase 2 CABP & GC studies

NCT 02210325

Delafloxacin (Hook, STD 2019; 46: 279-286)

- Delafloxacin 900mg oral
- Active Control: Ceftriaxone 250mg IM single dose (azithromycin was administered at the test-of-cure visit for patients found to have *C. trachomatis* at baseline)
- Randomized 2:1; Sponsor blinded; noninferiority (10%)
- Had prior successful phase 2 CABP & ABSSSI studies

NCT 02015637

BOTH COMPOUNDS FAILED IN OVERALL ENDPOINT, ALTHOUGH THE MAJORITY OF PATIENTS DID EXPERIENCE CURES WITH A SINGLE ORAL DOSE

SOLITHROMYCIN

- **Eradication**
- (genital micro ITT population)
  - Solithromycin 80.5% vs Ceftriaxone/azithro 84.5%
  - -4% (-13.6, 5.5)
- After removing patients who were lost to follow-up, the eradication rate for ceftriaxone/azithromycin was 100%.

Microbiological Response at TOC (ME all sites)	Solithromycin N=106 % (n/N)	Ceftriaxone/ Azithromycin N=107 % (n/N)	Soli-Cef/Azi (95% CI)
Cure, Women	100% (5/5)	100% (5/5)	-
Cure, Men	90.9% (90/99)	100% (102/102)	-9.1 (-16.4, -4.8)
Cure, hetero male	95.2% (20/21)	100% (24/24)	-4.8 (-23, 9.7)
Cure, MSM	89.7% (70/78)	100% (78/78)	-10.3 (-19, -5.3)

Chen, et al. Lancet ID 2019, 19:833-842, Table 2

DELAFLOXACIN

- **Cure**
- (urogenital micro ITT population)
  - Delafloxacin 85.1% vs Ceftriaxone 91%
  - -5.9 (-13.18, 1.36)
- Cure for Ceftriaxone was 97% when the patients who were lost to follow-up were excluded

Microbiological Response at TOC (UMITT)	Delafloxacin N=228 % (n)	Ceftriaxone N=100 % (n)	Dela-Cef (95% CI)
Cure, Women	92.5% (37/40)	94.1% (16/17)	-1.6 (-15.5, 12.2)
Cure, Men	83.5% (157/188)	90.4% (75/83)	-6.9 (-15.1, 1.4)
Cure, Hetero male	92.7% (102/110)	91.7% (44/48)	1.1 (-8.1, 10.3)
Cure, MSM/bisexual	70.1% (54/77)	88.6 (31/35)	-18.4 (-33.1, -3.8)

Hook, et al. STD 2019; 46: 279-286, table 3

BOTH REPORTS CONCLUDE FOR EITHER PRODUCT THAT A SINGLE ORAL DOSE WAS INSUFFICIENT

NEED FOR BETTER PREDICTION OF RELEVANT TISSUE EXPOSURE OVER TIME

Chen, et al. Lancet ID 2019; 19:833-842

"….oral solithromycin as a single 1000 mg dose is not suitable as a first-line alternative to combination ceftriaxone plus azithromycin. Additional studies would be required to assess the efficacy of multiple-dose solithromycin in the treatment of genital and extragenital gonorrhoea, including azithromycin-resistant *N gonorrhoeae.* …"

Hook, et al. STD 2019; 46: 279-286

"… the single 900-mg oral dose was not sufficient to provide sustained infection site exposure high enough for microbial eradication of *N. gonorrhoeae* with higher MIC values. Additional studies with alternative dosing regimens could be considered. It may be relevant for future studies of delafloxacin for gonorrhea to assess drug levels at different anatomic sites of infection using alternate dosing regimens to evaluate sufficiency of drug exposure…."

CHALLENGES IN DRUG DEVELOPMENT FOR UNCOMPLICATED GONORRHEA

- **Local PK data; understanding PKPD relationships**
  - Duration and level of exposure at the site of infection is key
    - Need antibiotic levels high enough and long enough to kill the bacteria
  - Need new non-clinical/clinical methods to understand exposure and assess potential dosing considerations
- **Patient population**
  - Consider the “tough to treat” resistant populations in Phase 2/3 trial design, ensuring the drug is properly challenged to address the greatest need
  - Need large enough sample size to fully assess; Always an issue in small phase 2 antibiotic trials
- **Dosing strategy**
  - Consider multiple doses or alternate formulations to overcome insufficient or variable exposure
  - Consider alternate treatment or treatment regimen based on risk of resistant bacteria
- **Development Funding and Commercial Viability**
- **Unique considerations for trials in gonorrhea**