OVERVIEW OF DRUG DEVELOPMENT CONSIDERATIONS FOR UNCOMPLICATED UROGENITAL GONORRHEA

A TALE OF TWO RECENT TRIALS

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Development Considerations of Antimicrobial Drugs for the Treatment of Gonorrhea
## TYPICAL ANTIBIOTIC DEVELOPMENT MILESTONES VS GONORRHEA*

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

**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

**Microbiologic Response at Test of Cure (TOC) visit** (Expectation ≥ 95%)
- Cure = Negative urogenital *N. gonorrhoeae* culture in patients positive at baseline
- Failure = Positive urogenital *N. gonorrhoeae* culture in patients positive at baseline; missing data; additional antibiotics
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%.

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

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


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

NEED FOR BETTER PREDICTION OF RELEVANT TISSUE EXPOSURE OVER TIME

“….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. …”

“… 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