Development of novel drugs for NG: translational challenges

FDA-CDC-NIAID Virtual Public Workshop

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Ricardo Chaves, MD, PhD

Executive Medical Director

Debiopharm International SA, Switzerland

Agenda

Development of novel drugs for *N. gonorrhoeae*: translational challenges

- Considerations on development of new drugs against NG
- Perspectives on Target Product Profile for NG
- Non-clinical activities up to IND
- Beyond IND: Translational PK/PD challenges

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Addressing the need for new antibacterials

- **Mission**: **Address unmet medical needs by leveraging FabI Inhibitors, a new class of antibiotics**[1]
  - **Novel MoA:** Disruption of the bacterial fatty acid biosynthetic pathway preventing bacterial growth
  - Very **low potential for spontaneous resistance development**[2] and **no cross-resistance** with other Ab
  - Potent and very narrow spectrum antibiotics with potential for **pathogen-specific therapy**[3]
  - Low off-target selection pressures and **preservation of gut microbiota**[4,5]
- **Most advanced FabI inhibitor**: **AFABICIN** in the treatment of **staphylococcal infections**
  - **Inactive against all nonstaphylococcal gram-positive and gram-negative pathogens**[3]
  - **Promising clinical activity** seen in ABSSSI - Phase II trial[6]
- **Preclinical Pipeline**:
  - New FabI inhibitor against ***N. gonorrhoeae*** incl. multi-resistant strains
  - New FabI inhibitor against ***A. baumannii*** incl. multi-resistant strains

CARB-X
Combating Antibiotic Resistant Bacteria

[1] Payne D et al. Antimicrob Agents Chemother 2002,[2] Kaplan N et al. Antimicrob Agents Chemother 2012,[3] Karlowski et al. Antimicrob Agents Chemother 2009
[4] Yao J et al. Antimicrob Agents Chemother 2016, [5] Nowakowska J et al. 28th ECCMID 2018 – Poster P0281 (Abstract No. 2471),[6] Wittke F et al. Antimicrob Agents Chemother 2020

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Considerations on development of new drugs against NG

General considerations

Development of new antibiotics for NG represents a high risk of failures for developers

1. **Rapid emergence** of *N. gonorrhoeae* **resistance** or decreased susceptibility[1,2]
   - Consistent problem after introduction of any new therapeutic antimicrobial for gonorrhea
2. **Limited knowledge** regarding the pharmacokinetics and pharmacodynamics of the available antimicrobials in the treatment of gonorrhea, particularly **extragenital sites**[1,2]
   - Pharyngeal infections are frequently asymptomatic but play a major role in resistance development[3]
3. **Multiple dose regimens** for gonorrhea might be required for difficult-to-treat extragenital infections[1,2]
   - However, single dose Directly Observed Therapy is preferred to ensure medications are delivered[1]
4. **Changes in the treatment guidelines** for NG infections are frequent and may be different across countries
   - Regulatory challenge for ongoing clinical programs
5. **Lack of knowledge** about **fundamental aspects on the pathogenesis/pathophysiology**
   - Debate on relevance of intracellular vs extracellular antibacterial activity for selection of drug candidates[2]

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[1] Unemo et al. Nat Rev Dis Primers 2019,[2] Theuretzbacher et al. Clin Microbiol Infect 2020,[3] Adamson PC & Klausner JD. Clin Infect Dis. 2021

Perspectives on TPP for NG

Target Product Profile

Perspectives on TPP for NG
Selected points for discussion

	Acceptable TPP	Ideal TPP
Indication	Treatment of Uncomplicated Urogenital *Neisseria gonorrhoeae* infections (susceptible and MDR)	First line treatment of Uncomplicated Urogenital, Ano-rectal and Oro-pharyngeal *Neisseria gonorrhoeae* infections (susceptible and MDR)
Target population	**Adults**	**Adults, adolescents**
Clinical Efficacy	Non-inferiority to current SoC	Non-inferiority to current SoC
Safety and Tolerability	Minimal outpatient monitoring required post treatment	No patient monitoring required post treatment
Route of administration	**Oral or IM**	**Oral and IM**
Dosing regimen	**Single Dose or Multiple Doses**	**One or two doses**
Treatment duration	**3-5 days**	**1 day**
***In vitro* activity**	Bactericidal/static, limited cross-resistance, low potential for emergence of cross-resistance	Bactericidal, intracellular activity, no cross-resistance, low potential for emergence of cross-resistance
Activity against extended spectrum cephalosporins and macrolide resistant strains	Yes	Yes
Drug Drug interaction profile	Minimal relevant DDIs including HIV and other STD treatments	No relevant DDIs including HIV and other STD treatments

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Non-clinical activities up to IND

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Non-clinical activities up to IND

Toxicology Work Package

Overview

- Standard, well-defined package as per ICH guidelines

Key points

- Duration of GLP toxicity studies varies across regions:
  - FDA may accept short duration studies, at least equivalent to intended treatment in FIH: quicker path to FIH, lower API amounts required
  - However, requirements from other regulatory bodies (e.g. EU) ask for 2 weeks treatment

➢ **Conducting only 2-week studies to support global development - most cost-effective option**

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Microbiology Work Package

Overview

- Standard NG susceptibility testing and culture are performed on agar media
- However, a number of conventional assays suggested by the guidances (MBC, killing curves, PAE) can only be performed in liquid cultures

Key points

- Several liquid media support NG growth, however the assay settings (e.g starting inoculum, growth kinetics) impact the model performance
    - Challenges in evaluating the comparative performance of different compounds
- Alternative approach of using surrogate organisms is not satisfactory
    - MoA / killing kinetics may not be identical across species

➢ **Data from liquid cultures should be considered exploratory and not essential**

Non-clinical activities up to IND

In vivo Efficacy Work Package

Overview

- Non-clinical NG programs mostly relied on surrogate models (e.g SA neutropenic mouse thigh) for PK/PD[1,2]
- Emerging evidence supports the use of the mouse vaginal NG infection model[3] as a PK/PD tool[4]
  - Promising model but has not been used as prospective translational PK/PD tool

Key points

- Recent internal data on a number of compounds suggest that **robust PK/PD** can be generated using the **mouse vaginal NG infection model**
  - Reproducible and quantitative dose-response
  - Identification of PK/PD index and magnitude associated with various bacterial endpoints

➢ **Robust data generated with this model should be considered appropriate for regulatory purposes**

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[1] Scangarella-Oman *et al*, Antimicrob Agents Chemother 2018
[2] Bradford *et al,* ACS Infect Dis 2020
[3] Jerse *et al*, Front. Microbiol. 2011
[4] Theuretzbacher *et al,* Clin Microbiol Infect 2020

Beyond IND

Translational PK/PD challenges

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Translational PK/PD challenges

Potential approaches to predict antibacterial activity in extragenital infection sites

Overview

- Relevant animal models for anorectal and pharyngeal infections are not (yet) available[1]

Key attributes to explore in the absence of models

- Appropriate physicochemical characteristics (e.g. cell permeability) during Lead Optimization
- Tissue distribution and penetration in infection sites (e.g. MALDI-MS, PBPK)
- Intracellular activity (currently only urethral/endometrial epithelial cell lines, PMNs models)
- Impact of treatment duration, despite limitations of current methodologies

➢ **Ongoing research and new developments are paramount to bridge the PK/PD gap for NG**

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[1] Conolly *et al*, Antimicrob. Agents Chemother. 2019

Contact information

Ricardo Chaves, MD, PhD
Executive Medical Director

Debiopharm International SA
info-international@debiopharm.com

Debiopharm™
Headquarters

Lausanne, Switzerland
www.debiopharm.com

Translational PK/PD challenges

PK/PD for urogenital NG infections

Approach*	Advantages	Drawbacks
Vaginal NG model	• Target pathogen • Increasing evidence supporting use for PK/PD	• Bacterial endpoints associated with clinical efficacy are not known • Different adhesion/invasion pathways vs human
Surrogate pathogen	• Approach already used for several programs • Supports efficacy in urogenital infections (stasis / 1 log kill)	• Intrinsic risk : different bacterial species • May not be feasible for narrow-spectrum antibiotics
Hollow fiber model	• Well suited to identify PK/PD driver • Uses target pathogen	• Bacterial endpoints associated with clinical efficacy are not known • No interplay with living organism

* Not an exhaustive list

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