(1) Submission ID#1527343

Pharmacodynamic evaluation of azithromycin in the treatment of gonorrhoea using a dynamic Hollow Fiber Infection Model simulating Neisseria gonorrhoeae infections

---

Author(s)

Susanne Jacobsson, n/a

Post-Doc

WHO Collaborating Centre for Gonorrhoea and Other STIs, National Reference Laboratory for Sexually Transmitted Infections, Department of Laboratory Medicine, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

Daniel Golparian, n/a

-

WHO Collaborating Centre for Gonorrhoea and Other STIs, National Reference Laboratory for Sexually Transmitted Infections, Department of Laboratory Medicine, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

Joakim Oxelbark, n/a

-

Division of Clinical Chemistry, Department of Laboratory Medicine, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

Role: Co-Author
Have you presented at either the 2022 or 2018 IPNC meetings?
No

Renata Maria Augusto da Costa, n/a

-

Global Antibiotic Research and Development Partnership (GARDP), Geneva, Switzerland

Francois Franceschi, n/a

-

Global Antibiotic Research and Development Partnership (GARDP), Geneva, Switzerland

David Brown, n/a

-

Institute for Therapeutic Innovation, College of Medicine, University of Florida, Orlando, FL, United States

Arnold Louie, n/a

-

Institute for Therapeutic Innovation, College of Medicine, University of Florida, Orlando, FL, United States

George Drusano, n/a

-

Institute for Therapeutic Innovation, College of Medicine, University of Florida, Orlando, FL, United States

Magnus Unemo, n/a

-

WHO Collaborating Centre for Gonorrhoea and Other STIs, National Reference Laboratory for Sexually Transmitted Infections, Department of Laboratory Medicine, Faculty of Medicine and Health, Örebro University, Örebro, Sweden, Institute for Global Health, University College London (UCL), London, United Kingdom

Background
Increasing incidence internationally in addition to the emergence and spread of antimicrobial resistance in Neisseria gonorrhoeae globally seriously threatens the management and control of gonorrhoea. In the absence of new treatment options understanding of the last remaining and currently used therapeutic antimicrobials are essential. Utilizing our dynamic in vitro hollow fiber infection model (HFIM), we examined the pharmacodynamics of azithromycin, against three N. gonorrhoeae reference strains, WHO X (extensively drug resistant, azithromycin [MIC=0.5 mg/l]), WHO U and WHO P (resistant to azithromycin [MIC=4 mg/l], otherwise susceptible) and one clinical isolate SE-716 (resistant to azithromycin [MIC=2 mg/l], otherwise susceptible).

Aim/Methods
The overarching aim was to examine the pharmacodynamics of azithromycin against N. gonorrhoeae in our dynamic in vitro HFIM. Due to the lack of a clinical azithromycin resistance breakpoint, a specific aim was to investigate if N. gonorrhoeae isolates with low-level resistance (MICs=2-4 mg/L), representing the vast majority of azithromycin-resistant isolates, are treatable with an azithromycin 2 g dose, which is recommended in several regions. Dose-range and dose-fractionation studies with azithromycin in the HFIM were performed. All experiments were followed up to 14 days.

Results
All examined strains grew well in the untreated growth control arms in the HFIM. Dose-range experiments showed that WHO X was successfully eradicated with a single 0.5 g dose, SE-716 with a single 2 g dose, while the single 2 g dose failed to eradicate both WHO U and WHO P. Azithromycin-resistant mutants were seen in the failed 1 g regime for SE-716 and the failed 2 g regime for WHO P displaying alterations in 23S rRNA gene. The dose-fraction experiments with the 2 g dose given as equally divided doses at q12 h and q6 h successfully eradicated WHO X, but failed to eradicate SE-716. SE-716 also displayed azithromycin-resistant mutants especially in the 1+1 g given as q12 h.

Conclusions
A clinical azithromycin resistance breakpoint is imperative. By using our dynamic in vitro HFIM, we show that N. gonorrhoeae isolates with azithromycin MIC=2 is treatable however, azithromycin needs to be administered as a 2 g single dose, for efficacy and suppression of resistance emergence.