Pre-clinical development of the natural compound antibiotic Corallopyronin A


Institute of Medical Microbiology and Parasitology, University Hospital Bonn, Bonn, Germany; German Center for Infection Research (DZIF), partner site Bonn-Cologne, Bonn, Germany; Department of Pharmaceutical Technology and Biopharmaceutics, University of Bonn, Bonn, Germany; Institute of Pharmaceutical Biology, University of Bonn, Bonn, Germany; Department of Microbial Drugs, Helmholtz Center for Infection Research, Braunschweig, Germany; DZIF, partner site Hanover-Braunschweig, Braunschweig, Germany; Translational Project Office, German Center for Infection Research, Braunschweig, Germany; Department of Microbial Natural Products, Helmholtz Institute for Pharmaceutical Research Saarland, Saarland, Germany; DZIF, partner site Hanover-Braunschweig, Braunschweig, Germany; WHO Collaborating Centre for Gonorhoea and Other STIs, Örebro, Sweden; Emory Antibiotic Resistance Center, Emory University School of Medicine, Atlanta, GA, USA; Institute for Pharmaceutical Microbiology, University of Bonn, Bonn, Germany

Abstract

Introduction: Corallopyronin A (CorA) inhibits bacterial DNA-dependent RNA polymerase. With its different mode of action, binding to the switch region, it is effective against rifampicin-resistant Staphylococcus aureus. CorA also kills Gram-negative Wolbachia, endobacteria of filarial nematodes, depletion of which results in worm sterility and death. Within the German Center for Infection Research (DZIF), www.dzif.de we are developing CorA to treat filarial infections.

Methods: CorA has successfully completed in vitro and in vivo efficacy studies and most standard in vitro and in vivo non-GLP ADME studies. Results: CorA does not alter the expression of CYP450s and CYP4A4 induction via PB is eight-fold lower than rifampicin. CorA has protein binding comparable to ibuprofen and is stable in plasma >240 min. Human and dog microsomes metabolize CorA slowly, t1/2 = 345 min (phase I reactions producing oxidation metabolites, minimal glucuronidation). The CorA EC50 for three off-target hits (A3 and P2Y1 receptors, CDK1 enzyme) are 170-1500-fold higher than the CorA in vitro effective concentration against Wolbachia. CorA does not inhibit hERG. No chromosomal damage in human lymphocytes was observed and CorA was Ames test negative. These results indicate that CorA is non-toxic and pharmacologically safe. Oral formulations using the amorphous solid dispersion principle increased the stability (>95% after 3 months at 30°C) and solubility of CorA that are well tolerated by rodents and canines. We have shown that CorA has efficacy against Chlamydia trachomatis infection and now demonstrated that it also impairs penicillin induced persistent C. trachomatis. CorA also has activity against the WHO and CDC panels of antimicrobial resistant Neisseria gonorrhoeae. The frequency of mutation in N. gonorrhoeae is low and no spontaneous mutants at 4X MIC have been selected. The frequency of mutation to resistance in S. aureus (strain HG001) is significantly lower (2.8 - 4.4-fold) than the rate determined with rifampicin.

Conclusions: CorA is a novel solution to several Global Health targets in the UN Sustainable Development Goals and WHO Priority Pathogen List requiring new antibiotics. We have funding from DZIF, BMBF and the EU to finalize the preclinical package, including formulation development and in vivo studies in two species to guide planning of the regulatory conform GLP studies. The manufacturing protocol - heterologous expression of Myxococcus xanthus and optimised DSP - has been transferred to a Contract Manufacturing Organization for up-scaling to produce pre-GMP and cGMP grade material for the GLP studies.

Efficacy

- Wolbachia endosymbionts of filarial worms
  - Depletes >98% of Wolbachia blocking development and killing worms
- Staphylococcus aureus
  - CorA is active against persistent C. trachomatis
  - N. gonorrhoeae are susceptible to CorA MIC 0.5-1 µg/ml
  - No spontaneous resistance seen in N. gonorrhoeae at 48 h (IC50: 100 µg/ml) (S. aureus is rate is 10³)
- Sexually transmitted infections (STIs)
  - Chlamydia trachomatis
    - Penicillin-induced persistent infection
    - CorA is active against persistent C. trachomatis
- Neisseria gonorrhoeae
  - CorA is active against persistent C. trachomatis

ADME

- CorA plasma stability
- CorA metabolism in microsomes

Toxicology

- In vitro / in vivo / in vitro
- CorA Rifampicin
  - Deoxy 
  - 10-7
  - 10-6
  - 10-5
  - 10-4
  - 10-3
  - 10-2
  - 10-1
  - 100
  - 101
  - 102
  - 2 log
  - 5 log
  - 8 log

Future plans

- PK/PD from Murine Thigh Infection Model (S. aureus/N. gonorrhoeae)
- Determine activity of CorA metabolites
- Feasibility study, CorA production with GMP certified CMO
- Dose range finding to identify the maximal tolerated dose in rats
- GLP safety pharmacology and in vivo toxicology in rodents and dogs
- Plan phase 1 trial with advice from BfArM

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Contact: Prof. Achim Hoerauf (Achim.Hoerauf@ukbonn.de); Dr. Kenneth Pfarr (Kenneth.Pfarr@ukbonn.de)