Z-3: Reducing risk of infection due to an MBL-producing organism by preventing acquisition of same

John H. Rex, MD
Chief Medical Officer, F2G Ltd;
Expert-in-Residence, Wellcome Trust
Operating Partner, Advent Life Sciences
Email: john.h.rex@gmail.com
Newsletter: http://amr.solutions

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Travelers are at risk for becoming colonized by ESBLs / CRE

- **Healthy Swedish travelers acquired ESBLs:** Tangden T, Cars O, Melhus A, Lowdin E. Foreign travel is a major risk factor for colonization with *Escherichia coli* producing CTX-M-type extended-spectrum β-lactamases: a prospective study with Swedish volunteers. AAC. 2010;54:3564-8.
  - Of 100 travelers, 24 acquired an ESBL during their travels
  - Of these, 25% were still carrying the ESBL 6 months later
- **Hospitalization is also a risk:** Eur Ctr for Dis Prevent Control. Carbapenemase-producing (OXA-48) *K. pneumoniae* ST392 in travellers previously hospitalised in Gran Canaria, Spain. 11 Jul 2018. (Accessed 30 July 2018 at https://ecdc.europa.eu/en/publications-data/carbapenemase-producing-oxa-48-klebsiella-pneumoniae-st392-travellers-previously)
  - The title says it all

In high-prevalence areas, a high fraction of CRE are MBL producers

- Mohanty S et al. Identification of carbapenemase-mediated resistance among Enterobacteriaceae bloodstream isolates: A molecular study from India. Indian J Med Microbiol. 2017;35(3):421-5.
  - 2/3rds of these CRE were NDM-1

- Peirano G et al. New Delhi metallo-β-lactamase from traveler returning to Canada. Emerg Infect Dis. 2011;17(2):242-4.
  - The title says it all

Z-3 is a

- (Hypothetical) non-absorbable pro-drug that lacks microbiologic activity in its pro-drug state.
- The prodrug conjugate is only hydrolysable by MBLs. This interaction is specific for the β-lactamase activity, and is not affected by human derived metallo-proteases
- Upon cleavage by an MBL in the periplasm, it releases peptide that kills the MBLa-expressing bacterium.
- Preclinical and Phase 1 data support daily dosing for up to 3 months

Phase 2 study of travelers from Northern Europe to SE Asia/India

- 200 healthy adults (50:50 M:F) from Northern Europe enrolled. All had travel plans for 4-8 weeks in SE Asia/India
- All were found to be free of ESBL- and MBL-producing strains of Enterobacteriaceae in rectal swab samples by culture on selective media and by next-generation meta-genomic sequencing
- They were randomized 1:1 to daily oral dosing with Z-3 vs. identical placebo beginning at the time of travel and for two weeks after their return

One month after return (two weeks after stop Z-3), rectal swabs tested

- 24% (24/100) of the subjects in both groups were found to carrying CRE in their stool
  - This is identical to the data from Tangden 2010

- 8% (8/100, rate taken as 1/3rd of CRE to reflect a range of travels) of the subjects in the placebo group and 0% (0/100) were found to be carrying an MBL
  - P = 0.04 by χ^2

Six months after return

- 6/24 (25%, identical to Tangden) of colonized subjects still carry the strain identified at 1-month, including 2 still carrying an MBL
  - Hence, persistent MBL rate is 2%

- Two infections occurred, one in each study arm. Both were uUTI in women and both were due non-CRE (non-ESBL, non-MBL)
  - Hence, 1/50 women developed uUTI during a 6-month observation.

Questions to debate

- Z-3 does not reduce infection rates but the infections that do occur can't be due an MBL if you're not carrying one
- Can (how can) these data be translated into a large-scale demonstration of utility?
- Is demonstration of reduced rates of infection due to MBL-producers required for proof of product efficacy?
  - If so, why? If not, why not?
  - NNT is ~1250 women if 1 in 50 women develop uUTI and the proportion due to an MBL is the mean of the 8% and 2% rates of MBL carriage at one and six months (50/0.04=1250).
  - Crude estimate is N = 30K (15K/arm) to prove reduced rate of uUTI due MBL in women
  - If this study is done, is the product only indicated for use in women?
- Would this product be accepted and used by payors (insurers, consumers, etc.)?