Multidrug-Resistant Gram-Negative Pathogens: New Strategies

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Agenda

- Review of compounds in development for gram-negative bacteria
  - Development stage maturity
  - Spectrum
  - Spectrum gaps
  - Mutant selection
  - Dosage forms
  - Safety

- Conclusions
Ceftazidime/Avibactam
(Forest Astra-Zeneca)

Ceftazidime (3rd generation cephalosporin) and NXL-104, a non-β-lactam class A and C beta-lactamase inhibitor

MOA: Cell wall synthesis

Microbiology

• Covers ESBL-producing Enterobacteriaceae and P. aeruginosa isolates producing class A and C β-lactamases, including KPC producers as well as AmpC-overexpressing strains

Spectrum Gaps

• Not active against bacteria producing metallo-lactamases, OXA or VEB ESBLs, OXA carbapenemases in A. baumannii, NDM-1 producers, and efflux-mediated ceftazidime resistance in P. aeruginosa

Mutant Selection: No data published

IV only

Safety

• Headache and GI effects (nausea/vomiting)

Stage of Development

• Phase 1 QTc study of 3000 mg CAZ/ 2000 mg AVI completed
• Phase 1 SAD & MAD phase 1 studies in Japanese subjects completed
• IV, Phase 2: cUTI (CAZ 500 mg/AVI 125 mg q8h) – 70.4% vs. 71.4% for imipenem in ME at TOC
• IV, Phase 2 cIAI (with metronidazole): 91.2% vs. 93.4% for meropenem
• Phase 1 3-way crossover study to assess IV PK and drug-drug interactions when CAZ/AVI and metronidazole are infused together
• (2) Phase 3 – 2000 mg CAZ/500 mg AVI + 500 mg metronidazole for cIAI; not yet recruiting
Ceftolozane (CXA-201) (Cubist)

CXA-101 (oxyimino-aminothiazolyl cephalosporin) + tazobactam (beta-lactamase inhibitor) (2:1 ratio)

**MOA:** cell wall synthesis

**Microbiology Coverage**
- P. aeruginosa ($\text{MIC}_{90} = 1\text{-}8 \mu g/ml$)
- CXA-101 is not a substrate of the MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY efflux pumps nor the carbapenem-specific porin OprD in P. aeruginosa

**Spectrum Gaps**
- Bacteria producing metallo-lactamases and certain ESBLs (OXA-15 and OXA-11, -14 and 16) confer losses of CXA-201 activity ($\text{MIC} >32 \mu g/ml$); derepression of ampC in P. aeruginosa can increase $\text{MIC}$ up to 8-fold; $\text{MIC}_{90}$ vs. MDR P. aeruginosa of >64 $\mu g/ml$
- Ceftazidime-R E. coli, K. pneumoniae ceftazidime-R or KPC producers, Enterobacter, Citrobacter, ESBL+ Proteus spp. ($\text{MIC}_{90}=16/16/16/16/16 \mu g/ml$)
- No activity against MRSA and other key gram-positives

**Mutant Selection** – 4-fold increase in $\text{MIC}$ on 3$^{rd}$ serial passage (one P. aeruginosa isolate)

**IV only**

**Stage of Development**
- Phase 2 cUTI (CXA-101 only) vs. ceftazidime (1g IV q8h): (129 in ITT; 82 in ME; 3/5 P.aeruginosa, 47/53 E. coli; 0/2 gram+)) → 2, Phase 3 recruiting: (1500 mg q8h)
- Phase 2: cIAI (1500/500 mg q8h) + metronidazole (500 mg q8h) vs. meropenem (1000 mg q8h) completed; 89% vs. 96% in clinical cure in ME population at TOC, respectively
- BAL/ELF study complete for CXA-101 - ELF concentrations 8 $\mu g/mL$, a concentration that inhibits 99 percent of P. aeruginosa for over 60 percent of the 8-hour dosing interval
- 2 (each), phase 3 recruiting for
  - cUTI/pyelonephritis: CXA-201 IV (1500mg q8h) vs. levofloxacin IV (750mg q24h) for 7 days
  - cIAI: CXA-201 IV (1500mg q8h) + metronidazole IV (500mg q8h) vs. meropenem IV (1000mg q8h) for 4-14 days
Fluorocycline tetracyclic antibiotic inhibiting protein synthesis

Spectrum

- **Gram-positives aerobes**: $\text{MIC}_{90} \leq 0.5 \, \mu\text{g/ml}$ vs. all gram-positive pathogens
- **Gram-negatives aerobes**: $\text{MIC}_{90} \leq 2 \, \mu\text{g/ml}$ vs. all gram-negatives, including carbapenem-resistant K. pneumoniae, ESBL-producing Enterobacteriaceae, A. baumannii, S. maltophilia; P. mirabilis, $\text{MIC}_{90}$ of 4 $\mu\text{g/ml}$
- **Anaerobes**: $\text{MIC}_{90} \leq 1 \, \mu\text{g/ml}$ vs. B. fragilis and $\leq 4 \, \mu\text{g/ml}$ vs. other Bacteroides spp.; $\text{MIC}_{90} \leq 1 \, \mu\text{g/ml}$ for all other anaerobes

**Spectrum Gaps:**

- Pseudomonas aeruginosa, Burkholderia spp.

**Mutant Selection:** $10^{-9} - 10^{-10}$ for gram-positives (4 isolates/3 species); $10^{-8} - 10^{-10}$ for gram-negatives (2 isolates/3 species)

**IV/oral**

**Safety and ADME**

- Some nausea, but little emesis
- No other safety concerns yet identified

**Stage of Development**

- Completed phase 1 SAD and MAD IV studies
- Completed phase 1 SAD oral study; MAD oral studies completed
- Enrolling in phase 2 CA-cIAI, with expected completion of in-life 2Q 2012
Boron Leu-tRNA synthetase inhibitor

**Spectrum**

- **Gram-positives:** No coverage reported
- **Gram-negatives:** Broadly active against Enterobacteriaceae with $\text{MIC}_{90}$s of 1 µg/ml; $\text{MIC}_{90}$s of 4-8 µg/ml vs. Pseudomonas and Acinetobacter; $\text{MIC}_{90} = 4$ µg/ml vs. Stenotrophomonas maltophilia, $\text{MIC}_{90} = 0.5$ µg/ml vs. N. gonorrhoae
- **Atypicals:** ?
- **Anaerobes:** Coverage of B. fragilis ($\text{MIC}_{90} = 4$ µg/ml) and others ($\text{MIC}_{90} = 1-8$ µg/ml)

**Spectrum Gaps:** Burkholderia

**Mutant Selection:** $10^{-7} - 10^{-8}$ across all species

**Safety Findings**

- Humans, reversible effect on reticulocytes; preclinical safety red blood cells

**Stage of Development**

- Completed Phase 1 SAD and MAD studies with oral and IV and mass balance with IV
- Suspended studies
  - IV, phase 2 for cUTI and cIAI (750 and 1500 mg q12h)
  - Single and multiple supratherapeutic IV doses in healthy Japanese and Caucasian subjects
Neoglycoside derived from sisomicin

**Spectrum**

- **Gram-positives:** 2 µg/ml vs. MRSA; Streptococci and enterococci are intrinsically resistant to aminoglycosides
- **Gram-negatives:** ESBL-producing Enterobacteriaceae (E. coli, K. pneumoniae, Serratia spp., P. mirabilis, Enterobacter spp.) have MIC$_{90}$s of 1-4 µg/ml; P. aeruginosa MIC$_{90}$ = 4-32 µg/ml; Acinetobacter MIC$_{90}$ = 32-64 µg/ml

**Spectrum Gaps:** Activity compromised by some aminoglycoside-modifying enzymes in A. baumannii and Providencia stuartii, indole$^+$ Proteus, expression of AdeB efflux pump in some A. baumannii strains, and 16S ribosomal methylase found frequently in NDM-1 Enterobacteriaceae

**Mutant Selection:** No data available

**IV only**

**Safety and ADME**

- Lack of nephrotoxicity or ototoxicity at 15 mg/kg; some tinnitus in phase 1
- Short T½ (2-3 h), 80-90% recovery in urine

**Stage of Development**

- Completed phase 1 SAD and MAD studies
- Completed phase 1 study for lung penetration
- PK study in renally impaired subjects nearing completion
- QTc evaluation recruiting
- cUTI/pyelonephritis: Phase 2 (15 mg/kg q24h x 5 d vs. IV levofloxacin 750 mg q24h) nearing completion
Fifth-generation cephalosporin + NXL104, a non-β-lactam β-lactamase class A and C inhibitor

- **Gram-positives:** MRSA, VRSA, MRSE, VRE (E. faecalis, amp-sensitive), S. pneumoniae, S. pyogenes
- **Gram-negatives:** H. influenzae, M. catarrhalis, ESBL-producing Enterobacteriaceae, wild type Acinetobacter, KPC-producers
- **Atypicals:** No coverage
- **Anaerobes:** No, requires combination with metronidazole

**Spectrum Gaps:** Acinetobacter producing OXA β-lactamases, Enterobacteriaceae producing metallo-β-lactamases, P. aeruginosa producing AmpC or with reduced outer membrane permeability, amp-resistant E. faecalis

**Mutant Selection:** Frequencies for stable mutants from 25 enterobacteria with ESBL, AmpC or KPC β-lactamases were mostly < $10^{-9}$
- Stable E. coli mutant had CTX-M-15 sequence change (Lys237Gln), with MIC change from < 0.06 to 8 μg/ml; this strain became more susceptible to other oxyimino-cephalosporins.
- 2 stable single-step mutants were from an AmpC-derepressed E. cloacae (MICs rose from 1 to 16 - >64 μg/ml) and had porin loss or AmpC sequence change

**IV only**

**Safety:** Headache and GI effects

**Stage of Development**
- Phase 1 QTc study of 1500 mg CEF/2000 mg AVI completed
- Phase 2 (recruiting): cUTI (CEF 600 mg /AVI 600 mg q8h or q12h vs. 500 mg doripenem q8h)
Siderophore Sulfactam, monobactam antibiotic

**MOA:** PBP binding, cell wall synthesis inhibition

**Microbiology (in presence of iron chelator to induce iron uptake systems)**
- $\text{MIC}_{90} \leq 4 \mu g/ml$ vs. strains with $\beta$-lactamase-R phenotype: *K. oxytoca*/Proteus/Providencia/Serratia/Acinetobacter/Burkholderia/Stenotrophomonas
- BAL30072 was active, at $\text{MIC}_{90} = <16 \mu g/ml$ vs. *P. aeruginosa* with derepressed AmpC and with most acquired $\beta$-lactamases
- Synergistic with meropenem (and other penems) vs. MDR NDM-1 species

**Spectrum Gaps**
- *P. aeruginosa* strains with efflux upregulated are problematic
- Strain-dependent: TEM-3/5, SHV-5
- *K. pneumoniae* with KPC-2,TEM-1, SHV-2 enzymes
- Strains containing PER-1 and rare OXA types
- Strains with $\beta$-lactamase-R phenotype: *E. coli*, *C. freundii*, *E. aerogenes*, *E. cloacae*, *K. pneumoniae* ($\text{MIC}_{90} >32; 16; 16; >32; >32$)

**Mutant Selection** - Resistant strains are obtained through serial passage (after 4-20 passages) for a various species (overexpressors of $\beta$-lactamase)
- Single-step mutants in *P. aeruginosa* at $10^{-6}$ – $10^{-8}$
- No mutant with an acquired deficiency in *tonB* or a siderophore receptor has been identified

**IV only**

**Safety and PK**
- Short $T\frac{1}{2}$ (1-3 h), 50% in urine

**Stage of Development**
- IV Phase 1 SAD (500 ml infusion 1-2.5 h, 500-8000 mg) completed
- MAD has completed, but another phase 1 study is planned to investigate additional dosage regimens
B-lactamase Inhibitor (active against class A and class C carbapenemases) to be used in conjunction with imipenem

**Spectrum with Imipenem**
- **Gram-positives:** streptococci, MSSA, MSSE, non-VRE
- **Gram-negatives:** At 4-8 µg/ml MK-7655, imipenem MICs of all strains were below the resistant breakpoint of IPM for Pseudomonas and Klebsiella containing KPCs
- **Atypicals:** No coverage
- **Anaerobes:** Coverage of B. fragilis and others

**Spectrum Gaps:** VRE, MRSA, Stenotrophomonas spp., Burkholderia spp. strains containing class D metalloproteases; high levels of AmpC or KPC; certain class A β-lactamases

**Mutant Selection:** $10^{-8}$ - $10^{-9}$ for 2 isolates of P. aeruginosa; $2 \times 10^{-7}$ to $<3 \times 10^{-8}$ for KPC+ K. pneumoniae for imipenem + MK-7655

**IV only**

**Preclinical Findings**
- Restored activity of imipenem to kill rapidly
- Low protein binding (20%)
- Active in delayed therapy pulmonary murine models with P. aeruginosa

**Stage of Development**
- Completed Phase 1 – dose-proportional PK; 125 mg x QID achieved targeted $\text{AUC}_{0-\text{inf}}$ of 37.5 µM·h and was unaffected by coadministration of imipenem (and vice versa)
Novel drugs for bad bugs are emerging, but few represent new mechanisms of action

The majority were initially discovered or had early development activities at biotech companies

All antibiotics currently in development have some holes in their spectrums against MDR gram-negative pathogens

The resistance armamentarium of successful clones is growing and appears not yet to be tapped out

Several antibiotics (TP-434, GSK2251052, plazomicin) are also under evaluation for potential use in treatment of severe respiratory disease caused by biothreat pathogens

- Bipartisan WMD Terrorism Research Center concluded that a terrorist armed with an antibiotic-resistant pathogen could produce a large-scale event with “catastrophic consequences,” resulting in a “potentially uncontrollable number of illnesses and/or deaths,” “civil and political unrest in the affected region,” and a “global economic impact”
Please note…

- Compounds in the preclinical stage were not highlighted.
- References for the data on each compound were not provided due to limitation of space, but the vast majority of information came from posters or publications, company websites, and www.clinicaltrials.gov.