Novel Antimicrobials

Prepared by: Daitiara Perez, PharmD
Cleveland Clinic Florida PGY1
DCPA 2016

Objectives

- Summarize the mechanism of action, pharmacokinetics, and pharmacology of novel antimicrobials
- Review indications and places in therapy in which novel agents may be beneficial
- Compare and contrast novel antimicrobials to commonly used agents for similar treatments

Dalbavancin (Dalvance®)
Coverage
Staphylococcus aureus (MSSA + MRSA)
Streptococcus agninosus
Streptococcus pyogenes
Streptococcus agalactiae
GRAM + ONLY

Clinical Trial
- Two phase 3 trials
  - Randomized, double-blind, double-dummy
  - n=1312 study subjects
- Intervention
  - Dalbavancin group
    - 1000mg IV one time infusion followed by a 500mg IV infusion 7 days later
  - Control group
    - Vancomycin 1000mg or 15mg/kg q12hours
      - After 3 days had the option to switch to linezolid

Drug Trial Overview
- Type of infections:
  - Cellulitis, major abscesses, and wound infections
- Primary Outcomes
Pharmacology and Pharmacokinetics

- MOA: Interferes with cell wall synthesis
- Semisynthetic lipoglycopeptide
- Minor metabolite has been excreted in the urine of study subjects but not measured in the plasma
- Evenly excreted through urine and feces (30% and 20%, respectively)
- ~346 hours half life
- No significant drug interactions (DI)

Approved Indications

- Acute bacterial skin and skin structure infections (ABSSSI)
  - Two-step regimen:
    1. 1000mg IV over 30 minutes one time
    2. 500mg IV over 30 minutes one time
  - One week after first infusion
  - Renal adjustment necessary once CrCl < 30 ml/min
- Available formulations
  - Solution available for injection 500mg/vial

Adverse Events

- Most common adverse reactions:
  - Diarrhea
  - Nausea
  - Headache
Warning and Precautions

- Hypersensitivity reactions
  - Possible cross-sensitivity with other glycopeptides
- Infusion-related reactions
- Hepatic effects
- Clostridium difficile-associated diarrhea

Therapeutic Application

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing regimen</td>
<td>Hepatic impairment</td>
</tr>
<tr>
<td>Less nephrotoxic</td>
<td>Lacks Enterococcus sp.</td>
</tr>
<tr>
<td>Minimal DI</td>
<td>Only available IV</td>
</tr>
<tr>
<td>Community use (30 min infusion)</td>
<td></td>
</tr>
</tbody>
</table>

Tedizolid (Sivextro®)
Coverage

Staphylococcus aureus (MSSA + MRSA)
Streptococcus anginosus
Streptococcus pyogenes
Streptococcus agalactiae
Enterococcus faecalis and faecium

GRAM + ONLY

Drug Trial Overview

- Two phase 3 trials
  - Randomized, double blind
- n = 1315 study subjects
- Intervention
  - Tedizolid group
    • 200mg PO once daily for 6 days
  - Control group
    • Linezolid 600mg PO every 12 hours

Drug Trial Overview

- Type of infections:
  - Cellulitis, major abscess, and wound infection
- Primary Outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>ITT</th>
<th>P 1</th>
<th>Treatment Difference (ITT-ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td>282 (31.3)</td>
<td>281 (31.5)</td>
<td>-0.1 (95% CI: -1.1, 0.9)</td>
</tr>
<tr>
<td>CE</td>
<td>282 (31.3)</td>
<td>281 (31.5)</td>
<td>-0.1 (95% CI: -1.1, 0.9)</td>
</tr>
<tr>
<td>Part 1</td>
<td>282 (31.3)</td>
<td>281 (31.5)</td>
<td>-0.1 (95% CI: -1.1, 0.9)</td>
</tr>
<tr>
<td>CE</td>
<td>282 (31.3)</td>
<td>281 (31.5)</td>
<td>-0.1 (95% CI: -1.1, 0.9)</td>
</tr>
</tbody>
</table>

ITT = intent-to-treat, P 1 = per-protocol, 95% CI = 95% confidence interval
Pharmacology and Pharmacokinetics

- MOA: Inhibition of protein synthesis
- Oxazolidinone class antibacterial agent
  - Pro-drug
- Bioavailability is 91%
  - IV to PO conversion is 1:1
- No significant metabolites besides the activated drug
- Primarily metabolized by the liver
- ~ 12 hour half life

Approved Indications

- ABSSSI
  - 200mg IV or PO once daily for 6 days
- No hepatic or renal adjustments necessary
- Available Formulations
  - Tablet (200mg)
  - Solution for injection
    - 200mg/vial

Adverse Events

- The most common adverse reactions:
  - Nausea
  - Headache
  - Diarrhea
  - Vomiting
  - Dizziness
Warnings and Precautions

- Patients with neutropenia (neutrophil count < 1000 cells/mm³) were not included in the original study
- Clostridium difficile-associated diarrhea

Therapeutic Application

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional oral therapy for MRSA, possible VRE?</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Once daily dosing</td>
<td>MAOI interactions</td>
</tr>
<tr>
<td>IV to PO 1:1 conversion</td>
<td>Only indicated for ABSSSI</td>
</tr>
<tr>
<td>Less risk of serotonin syndrome (ongoing clinical trials/case reports)</td>
<td></td>
</tr>
</tbody>
</table>

Oritavancin (Orbactiv®)
Coverage

Staphylococcus aureus (MSSA and MRSA)
Streptococcus dysgalactiae
Streptococcus pyogenes
Streptococcus agalactiae
Streptococcus anginosus group
Enterococcus faecalis (VREF)

GRAM + ONLY

Clinical Trial

- Two phase 3 trials
  - Randomized, double-blind, multi-center
- \( n = 1987 \) study subjects
- Intervention
  - Oritavancin group
    - Single 1200mg IV dose
  - Control group
    - Vancomycin 1000mg or 15mg/kg every 12 hours for 7-10 days

Clinical Trial

- Type of Infections:
  - Cellulitis, major cutaneous abscesses, and wound infections
- Primary Outcome
Pharmacology and Pharmacokinetics
- MOA: Inhibition of cross-linking and cell membrane disruption
- Semisynthetic lipoglycopeptide
- Weak inhibitor of CYP2C9 and CYP2C19
- Weak inducer of CYP3A4 and CYP2D6
- ~ 245 hours half life
- Minimal DI
  - Mainly medications with narrow therapeutic windows that are metabolized through CYP enzymes

Approved Indications
- ABSSSI
  - 1200mg IV over 3 hours one time
- No renal or hepatic dose adjustments necessary
- Available formulations
  - Powder solution for Injection
    - 400mg/vial

Adverse Events
- Most commonly reported adverse reactions:
  - Headache
  - Nausea
  - Vomiting
  - Limb and subcutaneous abscesses
  - Diarrhea
- Contraindication
  - Intravenous Unfractionated Heparin Sodium
Warning and Precautions

- Potential risk of bleeding with concomitant use of warfarin
  - Can falsely elevate international normalized ratio (INR) for up to 24 hours
- Coagulation test interference
  - Falsely elevates activated partial thromboplastin time (aPTT) for 48 hours
  - Falsely elevates prothrombin time (PT) and INR for 24 hours
- Hypersensitivity reactions
  - Cross-reactivity with other glycopeptide antibiotics

Warning and Precautions

- Infusion-related reactions
- Clostridium difficile-associated diarrhea
- Osteomyelitis

Therapeutic Application

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional MRSA coverage</td>
<td>Additional adverse effects:</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis</td>
</tr>
<tr>
<td></td>
<td>Coagulation interference</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td>Only indicated for ABSSSI</td>
</tr>
<tr>
<td>Less nephrotoxic</td>
<td></td>
</tr>
<tr>
<td>Community use (single infusion)</td>
<td></td>
</tr>
</tbody>
</table>
Telavancin (Vibativ®)

Coverage

- *Staphylococcus aureus* (MSSA + MRSA)
- *Streptococcus anginosus*
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Enterococcus faecalis* (VRE)

GRAM + ONLY

Clinical Trial

- Two phase 3 trials
  - Randomized, double blind
- n= 1867 study subjects
- Intervention
  - Telavancin Group
    - 10mg/kg IV q 24 hours
  - Control Group
    - Vancomycin 1000mg IV q12hours
Clinical Trial

- Type of infection:
  - Major abscess, wound infection, cellulitis, burn, and ulcer
  - Hospital and ventilator acquired bacterial pneumonia (HABP/VABP)

- Primary Outcome

| MOA: Inhibits cell wall synthesis |
| Synthetic lipoglycopeptide |
| No detectable metabolites |
| No significant metabolism |
| Excretion primarily through kidney (76% recovered from urine) |
| ~ 8 hour half life |
| No significant DI |
**Approved Indications**

- **Complicated skin and skin structure infection (CSSSI)**
  - 10mg/kg IV over 60 minutes every 24 hours for 14 days
- **HABP/VABP**
  - 10mg/kg IV over 60 minutes every 24 hours for 21 days

**Renal dose adjustments required**

- Dosing data not available for those with CrCl < 10ml/min or on hemodialysis

**Available Formulations**

- Solution for injection
  - 250mg/vial
  - 750mg/vial

**Adverse Events**

- Most common adverse reactions:
  - Nausea
  - Vomiting
  - Diarrhea
  - Taste disturbance
  - Foamy urine

- **Contraindications:**
  - Intravenous Unfractionated Heparin Sodium
  - Hypersensitivity to telavancin
  - Cross-reactivity with vancomycin unknown
**Warning and Precautions**

- Decrease efficacy among patients with moderate/severe pre-existing renal impairment
- Hypersensitivity reactions
- Infusion-related reactions
  - Needs to be administered over 60 minutes
  - "Red-man syndrome"

**Warning and Precautions**

- Clostridium difficile-associated disease
- Coagulation test interference
  - Falsely elevates PT, INR, and aPTT
- QTc prolongation

**Black Box Warning**

- Use in moderate/severe renal impairment (CrCl < 50ml/min) should only be considered if benefit outweighs risk
- Increased mortality observed
- Nephrotoxicity
- Avoid use in pregnancy
  - Potential risk to the fetus
  - Pregnancy test should be administered prior to initiation of therapy
- REMS program
  - Medication Guide
  - Communication Plan
Therapeutic Application

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional MRSA coverage</td>
<td>Only available IV</td>
</tr>
<tr>
<td>Effective against lung infections</td>
<td>QTc prolongation</td>
</tr>
<tr>
<td>Less monitoring required?</td>
<td>More nephrotoxic</td>
</tr>
<tr>
<td></td>
<td>CI pregnancy</td>
</tr>
<tr>
<td></td>
<td>Coagulation test interference</td>
</tr>
</tbody>
</table>

Gram + Coverage Summary

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Dalbavancin</th>
<th>Tedizolid</th>
<th>Oritavancin</th>
<th>Telavancin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage</td>
<td>MRSA</td>
<td>MRSA + VRE</td>
<td>MRSA</td>
<td>MRSA</td>
</tr>
<tr>
<td>Indication</td>
<td>ABSSSI</td>
<td>ABSSSI</td>
<td>ABSSSI</td>
<td>CSSSI + HABP/VABP</td>
</tr>
<tr>
<td>Dosing Regimen</td>
<td>Two single IV</td>
<td>IV or PO for 6 days</td>
<td>One time IV</td>
<td>IV for 14-21 days</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Comparator</td>
<td>Vancomycin</td>
<td>Linezolid</td>
<td>Vancomycin</td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>

Finafloxacin (Xtoro®)
Coverage

Pseudomonas aeruginosa
Staphylococcus aureus
GRAM + and GRAM -

Clinical Trial

- Two phase 3 trials
  - Randomized, multi-center
- n=560 study subjects
  - Included ages 6 months to 85 years
- Intervention
  - Finafloxacin 0.3% otic suspension group
    - Instill 4 drops twice daily to each ear for 7 days
  - Control group
    - Placebo (vehicle solution) same dosing

Type of infection:
- Acute otitis externa

Primary Outcome
Pharmacology and Pharmacokinetic
- MOA: Inhibits DNA-gyrase and unlinks double stranded DNA
- Quinolone antimicrobial agent
- 0.3% otic suspension
- Minimal serum plasma levels reached after otic administration
- Cross-resistance with other quinolones has been shown

Approved Indications
- Acute otitis externa (AOE)
  - Instill 4 drops in the affected ear twice daily for 7 days
- Available formulations
  - 0.3% otic suspension
    - 5mL bottle

Adverse Events
- Most common adverse reactions:
  - Pruritus of the ear
  - Nausea
**Warnings and Precautions**

- Prolonged use may lead to the development of resistant organisms
- Hypersensitivity reactions
  - Cross-reactivity with other quinolone antimicrobial agents

**Therapeutic Application**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>New antibiotic for AOE</td>
<td>Dosing regimen</td>
</tr>
<tr>
<td>Better than current standard of care</td>
<td></td>
</tr>
</tbody>
</table>

**Ceftolozane/tazobactam (Zerbaxa®)**
Coverage

Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Bacteroides fragilis
Pseudomonas aeruginosa
Streptococcus anginosus
Streptococcus constellatus
Streptococcus salivarius

GRAM + and GRAM -

Clinical Trial

- Two Phase 3 trial
- Randomized, double-blind
- n = 2047 study subjects
- Intervention
  - Ceftolozane/tazobactam group
    - 1.5g IV over 1 hour every 8 hours
  - Control group
    - Levofloxacin 750mg IV qdaily (cUTI)
    - Meropenem 1g IV q8 hours (cIAI)

Clinical Trial

- Type of infections
  - Complicated intra-abdominal infections (cIAI)
    - Appendicitis, cholecystitis, diverticulitis, gastric/douodenal perforation, abscesses, peritonitis
  - Complicated urinary tract infections (cUTI)
Clinical Trial

- **Primary Outcomes**

<table>
<thead>
<tr>
<th>Analysis Population</th>
<th>ZERBAXA® plus metronidazole % (N)</th>
<th>Meropenem % (N)</th>
<th>Treatment Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PITT</td>
<td>32/380 (10)</td>
<td>38/410 (9.7)</td>
<td>-6.1 (2.8, 7.4)</td>
</tr>
<tr>
<td>ME</td>
<td>38/375 (10.1)</td>
<td>80/612 (12.7)</td>
<td>-3.5 (1.4, 5.5)</td>
</tr>
</tbody>
</table>

* ZERBAXA 1 g plus metronidazole every 8 hours + meropenem 500 mg intravenously every 8 hours

Pharmacology and Pharmacokinetics

- **MOA:** Inhibition of cell wall biosynthesis
- **New cephalosporin in combination with an old beta-lactamase inhibitor**
- **No active metabolites formed**
- **Minimum metabolism**
- **Primarily excreted unchanged in the urine (95%)**
- **~ 3 hours half life**
- **No significant DI**
**Approved Indications**

- cIAI
  - Use in combination with metronidazole
  - 1.5g IV over 1 hour every 8 hours for 4-14 days depending on severity
- cUTI (including pyelonephritis)
  - 1.5g IV over 1 hour every 8 hours for 7 days
- Renal dose adjustments are necessary once CrCl < 50ml/min

**Available formulations**
- Powder for injection
  - 1.5g/vial

**Adverse Events**

- Most commonly reported adverse reactions:
  - Nausea
  - Diarrhea
  - Headache
  - Pyrexia

**Warnings and Precautions**

- Decreased efficacy in patients with a pre-existing renal impairment (CrCl < 50ml/min)
- Anaphylactic reactions
  - Patients with hypersensitivity to other beta-lactam antibacterial agents
- Clostridium difficile-associated diarrhea
Therapeutic Application

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>New agent to treat multi-drug resistant (MDR) pseudomonas</td>
<td>Only IV formulation</td>
</tr>
<tr>
<td>No QTC prolongation</td>
<td></td>
</tr>
</tbody>
</table>

Ceftazidime/avibactam (Avycaz®)

Coverage

- Enterobacter cloacae
- Enterobacter aerogenes
- Klebsiella oxytoca
- Klebsiella pneumoniae
- Pseudomonas aeruginosa
- Citrobacter koseri
- Citrobacter freundii
- Escherichia coli
- Proteus mirabilis
- Providencia stuartii

GRAM -
Clinical Trial

- Two phase 2 trials
  - Randomized, blinded, multi-center
- n=338 study subjects
- Intervention
  - Ceftazidime/avibactam group
    - 2.5g IV q 8 hours
  - Control group
    - Meropenem 1g IV q 8 hours

Clinical Trial

- Type of Infections:
  - cIAI
    - Specific infections were not listed
  - cUTI
- Primary Outcome
  - Not reported
  - Currently undergoing phase 3 trials

Pharmacology and Pharmacokinetics

- MOA: Inhibition of cell wall synthesis
- Cephalosporin antibacterial class with a novel (non beta-lactam) beta-lactamase inhibitor
- No active metabolites
- Primarily excreted unchanged in the urine (80%-90%)
- ~ 3 hours half life
- No significant DI
Approved Indications

- cIAI
  - Use in combination with metronidazole
  - 2.5g IV over 2 hour every 8 hours for 5-14 days depending on severity
- cUTI (including pyelonephritis)
  - 2.5g IV over 2 hour every 8 hours for 7-14 days
- Renal dose adjustments are necessary once CrCl < 50ml/min
- Available formulation
  - Powder for injection
    - 2.5g/vial

Adverse Events

- Commonly reported adverse reactions:
  - Vomiting
  - Nausea
  - Constipation
  - Anxiety

Warnings and Precautions

- Decreased efficacy in patients with pre-existing renal impairment (CrCl < 50ml/min)
- Hypersensitivity reactions
  - Cephalosporin cross-reactivity
  - Beta-lactam cross-reactivity
- Clostridium difficile-associated diarrhea
- Central nervous system reactions
Therapeutic Application

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative treatment for multi-drug resistant organisms (ESBLs, KPCs, CREs, etc)</td>
<td>Adverse effects: Seizures Anxiety</td>
</tr>
<tr>
<td>Less nephrotoxic than alternative agent (colistimethate)</td>
<td>Only IV formulation</td>
</tr>
<tr>
<td>Familiar antibiotic class</td>
<td></td>
</tr>
</tbody>
</table>

Adverse effects:
- Seizures
- Anxiety

Less nephrotoxic than alternative agent (colistimethate)

Familiar antibiotic class

Gram – Coverage Summary

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Ceftolozane/tazobactam</th>
<th>Ceftazidime/avibactam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage</td>
<td>MDR Pseudomonas</td>
<td>MDR Pseudomonas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KPCs CREs AmpCs</td>
</tr>
<tr>
<td>Indication</td>
<td>cIAI, cUTI</td>
<td>cIAI, cUTI</td>
</tr>
<tr>
<td>Dosing Regimen</td>
<td>q 8hours</td>
<td>q 8hours</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Comparator</td>
<td>Levofloxacin Meropenem</td>
<td>Meropenem</td>
</tr>
</tbody>
</table>

Question

- Ceftazidime/avibactam and Ceftolozane/tazobactam are both useful for treating multi-drug resistant pseudomonas infections.
- Answer: True
Question

- Telavancin currently has one black box warning related to fetal risk.
- Answer: False

Telavancin has 3 BBW:
Renal impairment
Nephrotoxicity
Fetal Risk

Question

- Tedizolid does not cover methicillin resistant staphylococcus aureus (MRSA) bacteria.
- Answer: False

Agent can be used to treat MRSA
References

- Dalbavancin [package insert] Chicago, IL; Durata therapeutics INC; 2014
- Telavancin [package insert] San Francisco, CA; Theravance Biopharma antibiotics INC; 2009
- Tedizolid [package insert] Ferentino, Italy; Merck and CO; 2014
- Finofloxacin [package insert] Forth Wort, TX; Novartis; 2014
- Ceftolozane/tazobactam [package insert] Cincinnati, OH; Forest Pharmaceuticals INC; 2015
- Ceftazidime/avibactam [package insert] Lexington, MA; Merck and CO; 2014

References

- Flanagan S., Bartizal K., Minasslan L., Fang E., etc; In vitro, in vivo, and clinical studies of tedizolid to assess the potential for peripheral or central monoamine oxidase interactions; AAC 57:7; 2013.