The new and coming oxazolidinones and glycopeptides: best for whom?

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PRESERVING OLD ANTIBIOTICS FOR THE FUTURE

RIEN A DECLARER

No conflicts of interest
New oxazolidinones and glycopeptides - outline

• The context:
  – methicillin-resistant \textit{Staphylococcus aureus} (MRSA) & vancomycin-resistant Enterococcus spp. (VRE) then & now

• The new oxazolidinones
  – \textit{tedizolid}, radezolid, MRX-I, LCB01-0371

• The new glycopeptides
  – \textit{dalbavancin}, oritavancin

• Integrating the new drugs: best for whom?
Antibacterial resistance  Us!  Antibiotic pipeline
“It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them...there is the danger that the ignorant man may easily underdose himself and, by exposing his microbes to nonlethal quantities of the drug, make them resistant.”

—Alexander Fleming

Nobel Prize Lecture, December 11, 1945.
MRSA: a timeline

**Background**

1940
- 30% of S. aureus is penicillin-R
- Fleming’s warning

1948
- First MRSA Isolated

1961
- First MRSA case

1981
- First CA-MRSA case

1997
- 50% MRSA in US hospitals
- “VRSA” isolated in Japan

1981
- Continued outbreaks

1988
- Dalbavancin
- Oritavancin

2000
- Mortality & cost cost

2015
- MRSA prevalence

**Interventions**

**NEW OXAZOLIDINONES**

**NEW GLYCOPEPTIDES**

**TARGET POPULATIONS**
VRE: a timeline

Regional Trends in Blood Culture VRE Rates

(GENTRY Program, 1997-2005 [9 years]; >10,000 isolates)

% Resistance

- 1997
- 1998
- 1999
- 2000
- 2001
- 2002
- 2003
- 2004
- 2005

EUROPE
LATIN AMERICA
UNITED STATES


*Not tested in a prevalence mode.

Fleming’s warning


by author
VRE: a timeline

1940
- Fleming’s warning

1960

1980
- 1986
  - First acquired VRE isolated in Europe

2000

2015
- 2013
  - Meta-analysis: median prevalence upon ICU admission 8%

NEW OXAZOLIDINONES
NEW GLYCOPEPTIDES
TARGET POPULATIONS

BACKGROUND

Ziakas et al. PLoS One 2013; http://dx.doi.org/10.1371/journal.pone.0075658

https://www.niaid.nih.gov/topics/antimicrobialresistance/examples/vre/Pages/overview.aspx
The cavalry has arrived.
Tedizolid (Sivextro®)

Linezolid:

Tedizolid:
Tedizolid’s history

• Created by Dong-A Pharmaceuticals (S. Korea)
• Acquired by Trius Therapeutics, which was
• Bought by Cubist, which was
• Bought by Merck
• Approved in USA in 2014, in Europe in 2015
  – Indication: acute bacterial skin & skin structure infections
• Ph3 trials ongoing for HAP & VAP

Theuretzbacher 2015: http://cddep.org/blog/posts/recent_fda_antibiotic_approvals_good_news_and_bad_news#
Tedizolid

- Tedizolid phosphate is the prodrug
- Tedizolid activated by plasma or intestinal phosphatases

Mechanism:
Like linezolid, binds to peptidyl transferase A-site of rRNA (50S subunit)
→ inhibits protein synthesis
Tedizolid

• Pharmacokinetics:
  – High **oral** bioavailability (86 – 100%)
  – Elimination: 80 – 90% feces, rest urine
  – Half-life: 12h
  – Volume of distribution: 70 L
  – Protein binding: 75-80% (linezolid: 30%)
  – Lung: humans: good penetration into ELF

• Pharmacodynamics:
  – concentration-dependent killing

• Dosing:
  – 600 mg p.o. or i.v. qd for six days (ABSSSI)

Rybak et al. *Infect Dis Ther* 2015; 4:1–14
Ong et al. *Drug Metab Dispos* 2014; 4:1275-84
Tedizolid: spectrum of activity

- Gram-positive only!
- *In vitro* potency against MRSA 2-8x higher than linezolid
  - But protein binding *in vivo* may offset its activity
- Cross-resistance with linezolid?
  - Modifications in the binding site for linezolid may be distinct
Tedizolid: spectrum of activity

<table>
<thead>
<tr>
<th>Strain</th>
<th>Source</th>
<th>Species</th>
<th>MIC (in μg/mL)</th>
<th>23S rRNA C2576T</th>
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<tbody>
<tr>
<td></td>
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<td>Linezolid</td>
<td>Tedizolid</td>
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<td>NRS127</td>
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<td>BEL Resources</td>
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<td>8</td>
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</table>

Tedizolid: clinical efficacy

Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial

Prof Gregory J Moran, MD, Edward Fang, MD, Prof G Ralph Corey, MD, Anita F Das, PhD, Carisa De Anda, PharmD, Dr Philippe Prokocimer, MD
Tedizolid: phase 3 design

**BACKGROUND**

NEW OXAZOLIDINONES

NEW GLYCOPEPTIDES

TARGET POPULATIONS

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**ESTABLISH 1 & 2 trial design**

**ESTABLISH 1 TRIAL:** All-oral course of SIVEXTRO vs linezolid (n=667)

**ESTABLISH 2 TRIAL:** IV/oral switch of SIVEXTRO vs linezolid (n=666)

**SIVEXTRO 200 mg**

- 6 days, once daily
- 4 days placebo

**Linezolid 600 mg**

- 10 days, twice daily

Days 0-10

---

**48-72 hours**

Primary endpoint—

Early clinical response:

**ESTABLISH 1**—No increase from baseline in lesion size and oral temperature of ≤37.6°C, confirmed by a second temperature measurement within 24 hours

**ESTABLISH 2**—At least a 20% decrease from baseline in lesion size

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**Days 18-25**

Secondary endpoint:

Investigator-assessed clinical response at post-therapy evaluation (7-14 days after the end of therapy)

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www.sivextro.com
Tedizolid: clinical efficacy

• Primary outcome: setting the bar low

“The primary efficacy outcome was early clinical response at the 48- to 72-hour assessment (no increase in lesion surface area from baseline and oral temperature of ≤37.6°C)...”
Tedizolid: clinical efficacy

• Early clinical response:
  – tedizolid 79.5% (95%CI 75 – 84%) - linezolid 79.4% (95%CI 75-84%)

• Sustained clinical response at end of treatment (D11):
  – tedizolid 69.3% (95%CI, 64–74%) - linezolid 71.9% (95%CI 67-77%)

• Similar responses in subset of 178 patients with confirmed MRSA infections
NEW OXAZOLIDINONES

Tedizolid: safety profile

• Pregnancy category C
• Difficult to find information in the literature

Choose your own adventure at www.sivextro.com...
BACKGROUND  NEW OXAZOLIDINONES  NEW GLYCOPEPTIDES  TARGET POPULATIONS

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SIVEXTRO safely and effectively. See full prescribing information for SIVEXTRO.

SIVEXTRO (tedizolid phosphate) for injection, for intravenous use SIVEXTRO (tedizolid phosphate) tablet, for oral use
Initial U.S. Approval: 2014

To reduce the development of drug-resistant bacteria and maintain the effectiveness of SIVEXTRO and other antibacterial drugs, SIVEXTRO should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

INDICATIONS AND USAGE
SIVEXTRO is an oxazolidinone-class antibacterial drug indicated in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria. (1)

DOSAGE AND ADMINISTRATION
200 mg administered once daily orally or as an intravenous (IV) infusion over 1 hour for six (6) days. (2.1)

DOSAGE FORMS AND STRENGTHS
• For injection: 200 mg, sterile, lyophilized powder in single-use vial for reconstitution for intravenous infusion;

FULL PRESCRIBING INFORMATION: CONTENTS*

CONTRAINDICATIONS
None (4)

WARNINGS AND PRECAUTIONS
• Patients with neutropenia: The safety and efficacy of SIVEXTRO in patients with neutropenia (neutrophil counts <1000 cells/mm³) have not been adequately evaluated. In an animal model of infection, the antibacterial activity of SIVEXTRO was reduced in the absence of granulocytes. Consider alternative therapies in neutropenic patients. (5.1)
• Clostridium difficile-associated diarrhea: Evaluate if diarrhea occurs. (5.2)

ADVERSE REACTIONS
The most common adverse reactions (≥2%) are nausea, headache, diarrhea, vomiting, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2015

www.sivextro.com
Selected Important Safety Information

Patients with neutropenia: The safety and efficacy of SIVEXTRO® (tedizolid phosphate) in patients with neutropenia (neutrophil counts <1000 cells/mm³) have not been adequately evaluated. In an animal model of infection, the antibacterial activity of SIVEXTRO was reduced in the absence of granulocytes. Alternative therapies should be considered when treating patients with neutropenia.

Clostridium difficile-associated diarrhea (CDAD), ranging from mild diarrhea to fatal colitis, has been reported with nearly all systemic antibacterial agents, including SIVEXTRO. Evaluate all patients who present with diarrhea following antibiotic use. Careful medical history is necessary because CDAD has been reported to occur more than two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibacterial use not directed against C. difficile should be discontinued, if possible.

Development of drug-resistant bacteria: Prescribing SIVEXTRO in the absence of a proven or strongly suspected bacterial infection or prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Adverse Reactions: The most common adverse reactions for SIVEXTRO are nausea (8%), headache (6%), diarrhea (4%), vomiting (3%), and dizziness (2%).
## Selected adverse reactions occurring in ≥2% of patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>SIVEXTRO (N=662)</th>
<th>Linezolid (N=662)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>
# Tedizolid: safety profile

## Incidence of hematological abnormalities

<table>
<thead>
<tr>
<th>Laboratory Assay</th>
<th>Potentially clinically significant values&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>SIVEXTRO (N=618)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Linezolid (N=617)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (&lt;10.1 g/dL [M]) (&lt;9 g/dL [F])</td>
<td></td>
<td>3.1%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Platelet count (&lt;112 x 10&lt;sup&gt;3&lt;/sup&gt;/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td></td>
<td>2.3%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Absolute neutrophil count (&lt;0.8 x 10&lt;sup&gt;3&lt;/sup&gt;/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td></td>
<td>0.5%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Male; <sup>b</sup>Female.  
<sup>a</sup>Values normal at baseline.  
<sup>b</sup>Represents lowest abnormal post-baseline value through the last dose of active drug.  
<sup>c</sup>Number of patients with non-missing laboratory values.
Tedizolid: cost

- 6 days of tedizolid p.o. = $2,212 (i.v. = $1,692)
- 10 days of linezolid po = $1,120

### AccessSIVEXTRO™ Enrollment Form

<table>
<thead>
<tr>
<th>PHONE: 1-844-282-4782</th>
<th>FAX: 1-844-282-4783</th>
</tr>
</thead>
</table>

1. SERVICES REQUESTED

- Patient Benefits Investigation, Prior Authorization, or Appeal
- Referrals to the Merck Patient Assistance Program ("PAP") (Please include a copy of the prescription with this form)

2. PATIENT INFORMATION

Name: ___________________________ Gender: ☐ Male  ☐ Female  Date of Birth ___/___/___
Address: ___________________________ City: ______ State: ______  ZIP: ______
Email: ___________________________ Home Phone: ______  Cell Phone: ______
Work Phone: ________________________

3. HEALTH CARE PROFESSIONAL INFORMATION (REQUIRED)

- Signature: ___________________________ Date: ______

www.sivextro.com

ESCMID eLibrary by author
Radezolid

- Oral synthetic oxazolidinone designed by Rib-X → Melinta Therapeutics
- 2007: Phase 2 trials for community-acquired pneumonia and uncomplicated bacterial skin infections
Radezolid

- No partner found; not further developed...

- www.melinta.com:
  “In January 2015, Melinta entered into a license agreement for the development and commercialization of radezolid in topical formulations for a variety of dermatological indications. Melinta retains the option to co-develop or fully regain rights to radezolid upon completion of specific development milestones.”
Dalbavancin

Vancomycin:

Dalbavancin:
Dalbavancin’s history

• Synthetic lipoglycopeptide
• Not really new!
  – 1987: described by researchers at Lepetit Research Center
    → Biosearch Italy → Vicuron → acquired by Pfizer...
    • clinical development not successful, no approval!
  – 2009: rights won by Durata, which repeated ph3 trials
    → 2014: acquired by Actavis
• Approved in USA in 2014, Europe in 2015
  – Indication: acute bacterial skin & skin structure infections
  – Trials ongoing for CA pneumonia (MRSA) & pediatric osteomyelitis
Dalbavancin

• Mechanism: binds to acyl-d-alanyl-d-alanine (peptidoglycan)

• Pharmacokinetics:
  – Dual elimination - urine & feces
  – **Half-life 150 - 250h (!)** → once weekly dosing
  – Volume of distribution 15.7 L
  – Protein binding: 98% (!)
  – i.v. only (poor oral absorption)
  – Lung: penetrates well in rats; humans??
  – CSF: almost undetectable in rabbits

• Pharmacodynamics:
  – Concentration-dependent killing (+ area under the curve)
Dalbavancin

• Spectrum of activity:
  – More potent *in vitro* activity than vancomycin & teicoplanin against Staphylococci & *Streptococcus pneumoniae* & *pyogenes*
    • Protein-binding
  – Not active against vancomycin-resistant *S. aureus*
  – *In vitro* activity against vancomycin-resistant Enterococci with *vanB* & *vanC* resistance genes, but not *vanA* (the most common!)
• Resistance
  – Not yet described clinically
  – Cross-resistance with other glycopeptides
Dalbavancin: clinical efficacy & safety
Dalbavancin: DISCOVER 1 & 2

- Identical trials done sequentially
- Double-blind, randomized, non-inferiority multicenter trials (56 & 84 sites)
  - Randomization in fixed blocks of four
- Dalbavancin (1g iv day 1, 500 mg iv day 8) vs. vancomycin/linezolid for 10 – 14 days in patients with ABSSSI
- Primary outcome = early clinical response (from 48h to 72 h, no increase in lesion surface area from baseline and oral temperature of ≤37.6°C)
Dalbavancin: clinical efficacy

- Pooled results:
  - Early treatment response:
    dalbavancin 240/288 (83.3%) vs. vanc/linezolid 233/285 (81.8%) (difference, 1.5%; 95%CI −4.6 to 7.9)

Dalbavancin: clinical efficacy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dalbavancin (N=652)</th>
<th>Vancomycin–Linezolid (N=651)</th>
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</thead>
<tbody>
<tr>
<td>Clinical response according to infection type</td>
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</tr>
<tr>
<td>Cellulitis</td>
<td></td>
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<tr>
<td>At 48–72 hr</td>
<td>238/354 (67.4)</td>
<td>269/349 (77.1)</td>
</tr>
<tr>
<td>At end of therapy</td>
<td>294/324 (90.7)</td>
<td>276/301 (91.7)</td>
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<tr>
<td>Major abscess</td>
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<tr>
<td>At 48–72 hr</td>
<td>133/163 (81.6)</td>
<td>149/173 (86.1)</td>
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<tr>
<td>At end of therapy</td>
<td>125/133 (94.0)</td>
<td>133/139 (93.7)</td>
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<tr>
<td>Traumatic wound or surgical-site infection</td>
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<tr>
<td>At 48–72 hr</td>
<td>111/142 (78.2)</td>
<td>103/131 (78.6)</td>
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<tr>
<td>At end of therapy</td>
<td>98/113 (86.7)</td>
<td>93/105 (88.6)</td>
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<tr>
<td>Investigator-assessed clinical response at end of therapy according to baseline pathogen</td>
<td></td>
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</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>187/191 (97.9)</td>
<td>171/177 (96.6)</td>
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<tr>
<td>Methicillin-resistant <em>S. aureus</em></td>
<td>72/74 (97.3)</td>
<td>49/50 (98.0)</td>
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<td><em>Streptococcus pyogenes</em></td>
<td>19/19 (100.0)</td>
<td>12/13 (92.3)</td>
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<tr>
<td>Clinical response at end of therapy according to diabetes mellitus status at baseline</td>
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<tr>
<td>Diabetes mellitus</td>
<td>60/71 (84.5)</td>
<td>67/76 (88.2)</td>
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<td>No diabetes mellitus</td>
<td>457/499 (91.6)</td>
<td>435/469 (92.7)</td>
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<td>Clinical response at end of therapy according to SIRS status at baseline</td>
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<tr>
<td>SIRS</td>
<td>257/296 (86.8)</td>
<td>263/290 (90.7)</td>
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<tr>
<td>No SIRS</td>
<td>260/274 (94.9)</td>
<td>239/235 (93.7)</td>
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### Table 4. Adverse Events.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dalbavancin (N=652)</th>
<th>Vancomycin–Lincozolid (N=651)</th>
<th>P Value*</th>
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</thead>
<tbody>
<tr>
<td>Any adverse event</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Any event — no. of patients (%)</td>
<td>214 (32.8)</td>
<td>247 (37.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Total no. of events</td>
<td>540</td>
<td>645</td>
<td>0.05</td>
</tr>
<tr>
<td>Treatment-related adverse event†</td>
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<td></td>
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</tr>
<tr>
<td>Any event — no. of patients (%)</td>
<td>80 (12.3)</td>
<td>89 (13.7)</td>
<td>0.45</td>
</tr>
<tr>
<td>Total no. of events</td>
<td>139</td>
<td>183</td>
<td>0.02</td>
</tr>
<tr>
<td>Serious adverse event — no. of patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>17 (2.6)</td>
<td>26 (4.0)</td>
<td>0.16</td>
</tr>
<tr>
<td>Treatment-related event†</td>
<td>2 (0.3)</td>
<td>4 (0.6)</td>
<td>0.41</td>
</tr>
<tr>
<td>Death — no. (%)</td>
<td>1 (0.2)</td>
<td>7 (1.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Treatment-limiting adverse event — no. of patients (%)§</td>
<td>14 (2.1)</td>
<td>13 (2.0)</td>
<td>0.85</td>
</tr>
<tr>
<td>Most common treatment-related adverse event — no. of patients (%)¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (2.5)</td>
<td>19 (2.9)</td>
<td>0.62</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (0.8)</td>
<td>16 (2.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (0.6)</td>
<td>15 (2.3)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Dalbavancin: safety

• 10-day half-life?
• Ecologic effects?
Dalbavancin: cost

- $1,490 per 500 mg vial \(\rightarrow\) one treatment = $4470
Oritavancin

Vancomycin:

Oritavancin:

Commons.wikimedia.org, orbactiv.com
Oritavancin’s history

• Not really new!
  – vancomycin derivate originally discovered and developed by Eli Lilly, where first development was discontinued (injection-sit reactions)
    → acquired by Targanta:
      completed Phase 3 trials but failed to achieve approval
    → acquired by the Medicine Company:
      successfully repeated ph3 trials
• Approved in USA in 2014, Europe in 2015
  – Indication: acute bacterial skin & skin structure infections
  – Trials ongoing for pediatric use

Theuretzbacher 2015: http://cddep.org/blog/posts/recent_fda_antibiotic_approvals_good_news_and_bad_news#
Oritavancin

- Mechanisms: binds to acyl-d-alanyl-d-alanine (peptidoglycan) AND depolarizes the cell membrane
- Pharmacokinetics:
  - Excreted unchanged in urine & feces
  - Half-life 393h → once weekly dosing
  - Volume of distribution 100 L
  - Protein binding: 90%
  - i.v. only (poor oral absorption)
  - ELF penetration < 3% (humans)
  - CSF 1-5% (rabbits)
- Pharmacodynamics:
  - Concentration-dependent killing
Oritavancin

• Spectrum of activity:
  – MICs for VISA & VRSA lower than for vancomycin but still above the preliminary PK/PD breakpoint
  – Enterococcus spp.: “no evidence of cross-resistance with with resistant phenotypes such as VanA, VanB, VanC, or VISA’’ but…

Theuretzbacher 2015: http://cddep.org/blog/posts/recent_fda_antibiotic_approvals_good_news_and_bad_news#
Oritavancin

Antibacterial Activity

Oritavancin has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections as described in the Indications and Usage section [see Indications and Usage (1.1)].

*Staphylococcus aureus* (including methicillin-resistant isolates)

*Streptococcus agalactiae*

*Streptococcus anginosus group* (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*)

*Streptococcus dysgalactiae*

*Streptococcus pyogenes*

*Enterococcus faecalis* (vancomycin-susceptible isolates only)

The following in vitro data are available but their clinical significance has not been established. At least 90% of isolates of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to 0.12 mcg/mL for oritavancin. However, the safety and effectiveness of oritavancin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

*Enterococcus faecium* (vancomycin-susceptible isolates only)
Oritavancin

• Resistance
  – Not yet described clinically, but mechanisms known:
    • current glycopeptide resistance mechanisms (e.g., van operons)
    • VISA-type cell wall thickening mechanism
Oritavancin: clinical efficacy & safety

Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections

G. Ralph Corey, M.D., Heidi Kabler, M.D., Purvi Mehra, M.D., Sandeep Gupta, M.D., J. Scott Overcash, M.D., Ashwin Porwal, M.D., Philip Giordano, M.D., Christopher Lucasti, M.D., Antonio Perez, M.D., Samantha Good, Ph.D., Hai Jiang, Ph.D., Greg Moeck, Ph.D., and William O’Riordan, M.D., for the SOLO I Investigators*
Oritavancin: SOLO I

- Double-blind, randomized, non-inferiority multicenter trial
- Oritavancin single dose (1200 mg iv) vs. vancomycin 7-10 days in patients with ABSSSI
- Primary outcome = early clinical response (from 48h to 72 h, no increase in lesion surface area from baseline nor oral temperature)

Oritavancin: clinical efficacy

**BACKGROUND**

**NEW OXAZOLIDINONES**

**NEW GLYCOPEPTIDES**

**TARGET POPULATIONS**

**Corey et al.**


![Figure 2. Primary and Secondary Efficacy End Points According to Analysis Population and MRSA Subgroup.](image-url)
Oritavancin: clinical efficacy

Table 2. Primary Efficacy Outcome at Early Clinical Evaluation According to Pathogen Detected at Baseline (Intention-to-Treat Population Who Could Be Evaluated Microbiologically). *

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Oritavancin (N = 244)</th>
<th>Vancomycin (N = 242)</th>
<th>Difference (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of at least one pathogen</td>
<td>201/244 (82.4)</td>
<td>196/242 (81.0)</td>
<td>1.4 (-5.5 to 8.3)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>180/220 (81.8)</td>
<td>172/210 (81.9)</td>
<td>-0.1 (-7.4 to 7.2)</td>
</tr>
<tr>
<td>MRSA</td>
<td>84/104 (80.8)</td>
<td>80/100 (80.0)</td>
<td>0.8 (-10.1 to 11.7)</td>
</tr>
<tr>
<td>MSSA</td>
<td>96/116 (82.8)</td>
<td>92/110 (83.6)</td>
<td>-0.9 (-10.6 to 8.9)</td>
</tr>
<tr>
<td>Streptococcus species</td>
<td>25/31 (80.6)</td>
<td>31/38 (81.6)</td>
<td>-0.9 (-19.5 to 17.6)</td>
</tr>
<tr>
<td>S. anginosus group†</td>
<td>12/13 (92.3)</td>
<td>14/16 (87.5)</td>
<td></td>
</tr>
<tr>
<td>S. agalactiae</td>
<td>6/7 (85.7)</td>
<td>8/8 (100.0)</td>
<td></td>
</tr>
<tr>
<td>S. pyogenes</td>
<td>5/8 (62.5)</td>
<td>5/10 (50.0)</td>
<td></td>
</tr>
<tr>
<td>S. dysgalactiae</td>
<td>2/3 (66.7)</td>
<td>3/3 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>6/7 (85.7)</td>
<td>4/5 (80.0)</td>
<td></td>
</tr>
</tbody>
</table>

*ESCMID eLibrary by author

Oritavancin: safety

- Pregnancy Category C

- Use of intravenous unfractionated heparin sodium is contraindicated for 5 days after ORBACTIV® administration because the aPTT test results are expected to remain falsely elevated for approximately 120 hours (5 days).

<table>
<thead>
<tr>
<th>Table 3. Patients with Adverse Events (Safety Population).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
</tr>
<tr>
<td>At least 1 adverse event that developed during treatment</td>
</tr>
<tr>
<td>Related to study drug</td>
</tr>
<tr>
<td>Leading to discontinuation of study drug</td>
</tr>
<tr>
<td>Serious adverse event†</td>
</tr>
<tr>
<td>Related to study drug</td>
</tr>
<tr>
<td>Leading to discontinuation of study drug</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>Most frequently reported adverse events‡</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Infusion-site reaction</td>
</tr>
<tr>
<td>Infusion-site extravasation</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Cellulitis</td>
</tr>
<tr>
<td>Pyrexia</td>
</tr>
</tbody>
</table>
Oritavancin: cost

- Around $3000 for one dose
Best for whom?
Some non-evidence-based conclusions

<table>
<thead>
<tr>
<th></th>
<th>OXAZOS</th>
<th>GLYCOPEPTIDES</th>
</tr>
</thead>
<tbody>
<tr>
<td>COST</td>
<td>😞</td>
<td>😞</td>
</tr>
<tr>
<td>SPECTRUM/ EFFICACY</td>
<td>😞</td>
<td>😞</td>
</tr>
<tr>
<td>SAFETY</td>
<td>😞</td>
<td>😞</td>
</tr>
<tr>
<td>ECOLOGIC EFFECTS</td>
<td>😞</td>
<td>😞</td>
</tr>
<tr>
<td>CONVENIENCE</td>
<td>😊</td>
<td>😊</td>
</tr>
</tbody>
</table>
Indicated for...

- Someone with an ABSSSI!
- Someone with MRSA – or whom you strongly suspect of carrying MRSA
- Glycopeptides:
  - Someone with dubious compliance – and yet someone who will contact you if any side effects
  - Someone whose hospitalization/home health care is difficult to arrange
Not indicated for...

- Someone without an ABSSSI
- Someone without any suspicion of MRSA
- Pregnant/lactating women
- Someone who can have linezolid, vancomycin, or teicoplanin
Thank you!

Individualized Medicine in Infectious Diseases: a Practical Approach, ESCMID Postgraduate Education Course

3 - 4 June 2016, Tübingen, Germany

Organizers

- ESCMID Parity Commission
- ESCMID PK/PD of Anti-Infectives Study Group (EPASG)
- ESCMID Study Group for Antibiotic Policies (ESGAP)