One-Hit Wonders: A New Era of Antibiotics?

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Pharmacy Grand Rounds
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Objectives

• Identify advantages and disadvantages of single-dose antibiotics

• Review the pharmacology of dalbavancin and oritavancin

• Discuss current evidence and the place in therapy of dalbavancin and oritavancin
Single-Dose Antimicrobials

• Route of administration
  • Penicillin G benzathine IM for syphilis

• Pharmacokinetics
  • Azithromycin for *Chlamydia trachomatis*

• Formulation
  • Azithromycin microspheres for CAP

CAP = Community-acquired pneumonia

Workowski KA. *Clin Infect Dis* 2015;61(Suppl 8).
Single-Dose Antimicrobials

Advantages

• Patient adherence
• Potentially reduced resistance
• Potential cost reductions
  • ↓ hospitalizations
  • ↓ hospitalized complications
• No need for long-term venous catheters
• No therapeutic drug monitoring

Single-Dose Antimicrobials

Disadvantages

- Standardized dosing
- May be lost to follow up
- Therapeutic drug monitoring
- Safety data
- Antimicrobial stewardship

Dalbavancin and Oritavancin

One-Hit Wonders?
Question 1

• Dalbavancin and oritavancin have broad spectrum activity against gram positive and gram negative bacteria including multidrug resistant organisms
  • True
  • False
  • I don’t know
Vancomycin

Dalbavancin

Oritavancin
Spectrum of Activity
*Staphylococcus* spp.

<table>
<thead>
<tr>
<th></th>
<th>MSSA</th>
<th>MRSA</th>
<th>hVISA</th>
<th>VISA</th>
<th>VRSA</th>
<th>DNSSA</th>
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</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>✓</td>
<td>✓</td>
<td>V</td>
<td>X</td>
<td>X</td>
<td>V</td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>V</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>Oritavancin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

V = variable

MSSA = Methicillin-sensitive *S. aureus*
MRSA = Methicillin-resistant *S. aureus*
hVISA = heterovariant Vancomycin-intermediate *S. aureus* (MIC=1-4)
VISA = Vancomycin-intermediate *S. aureus* (MIC=8-16)
VRSA = Vancomycin-resistant *S. aureus* (MIC≥32)
DNSSA = Daptomycin non-susceptible *S. aureus*

Spectrum of Activity
Other organisms

<table>
<thead>
<tr>
<th></th>
<th>Strep spp.</th>
<th>VSE</th>
<th>VRE</th>
<th>G+ anaerobes</th>
<th>Gram negatives</th>
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<tbody>
<tr>
<td>Vancomycin</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
<td>X</td>
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<tr>
<td>Dalbavancin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Oritavancin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
</tr>
</tbody>
</table>

V = variable

VSE = Vancomycin-sensitive *Enterococcus*
VRE = Vancomycin-resistant *Enterococcus*
# Kinetics & Dosing

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vancomycin</th>
<th>Dalbavancin</th>
<th>Oritavancin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life (h)</td>
<td>4-6</td>
<td>346</td>
<td>245</td>
</tr>
<tr>
<td>Clearance (L/h)</td>
<td>4.06</td>
<td>0.0513</td>
<td>0.445</td>
</tr>
<tr>
<td>Volume of distribution (L)</td>
<td>60.5</td>
<td>7-13</td>
<td>87.6</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>55</td>
<td>93</td>
<td>85</td>
</tr>
<tr>
<td>Elimination</td>
<td>Urine, 75% over 24h</td>
<td>Urine, 33% unchanged; feces, 20%</td>
<td>Urine, &lt; 5%; feces, &lt; 1%</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>--</td>
<td>--</td>
<td>InH: 2C9, 2C19; InD: 3A4, 2D6</td>
</tr>
<tr>
<td>Typical dosing</td>
<td>15 mg/kg IV q12h + TDM</td>
<td>1000mg IV day 1, 500mg IV day 8</td>
<td>1200mg IV once</td>
</tr>
<tr>
<td>Renal adjustments</td>
<td>Yes, dialyzable</td>
<td>Yes, non-dialyzable</td>
<td>No, non-dialyzable</td>
</tr>
</tbody>
</table>

InH = Inhibitor  
InD = Inducer  
TDM = Therapeutic drug monitoring

Once-Weekly Dalbavancin versus Daily Conventional Therapy for Skin Infection (DISCOVER 1 & DISCOVER 2)

Study Design and Treatment

DISCOVER 1 & 2

• **Design**
  - International, multicenter, randomized, double-blind, double-dummy phase 3

• **Intervention**
  - Dalbavancin 1gm IV on day 1 then 500mg IV on day 8
  - Vancomycin 15 mg/kg IV q12h x 10-14 days

• **Population**
  - ≥18 years of age
  - Acute bacterial skin and skin-structure infection
    - ≥ 1 systemic and ≥ 2 local signs of infection
    - Requiring ≥ 3 days of IV antibiotics

Efficacy and Safety Assessments
DISCOVER 1 & 2

• **Primary Outcome**
  • Treatment success at 48-72 hours after drug initiation
    • Cessation of spread of erythema
    • Resolution of fever

• **Secondary Outcomes**
  • Clinical response at end of therapy

• **Safety Outcomes**
  • Adverse events
  • Death

Treatment Success
DISCOVER 1 & 2

Vancomycin vs. Dalbavancin

DISCOVER 1
82% (95% CI: -4.6 to 7.9)

DISCOVER 2
78% (95% CI: -7.4 to 4.6)

Both Trials
80% (95% CI: -4.5 to 4.2)

*Absolute difference (95% confidence interval)

Secondary Endpoints
DISCOVER 1 & 2

MSSA = Methicillin-Susceptible S. aureus
MRSA = Methicillin-Resistant S. aureus

Study Critique
DISCOVER 1 & 2

• Strengths
  • Study design
  • Pooled analyses of both trials
  • Sensitivity analyses with type of infection and pathogen
  • Extended surveillance of adverse events

• Limitations
  • Subjective assessment of clinical response
  • Vancomycin fixed dosing and no TDM
  • Adherence in a monitored clinical setting
  • Low MRSA rates

TDM = Therapeutic drug monitoring

A Randomized Clinical Trial of Single-Dose Versus Weekly Dalbavancin for Treatment of Acute Bacterial Skin and Skin Structure Infection

Dunne MW et al. (2016)

- **Dose-exploration study in ABSSSI**
  - 1500mg IV once
  - 1000mg IV on day 1 then 500mg IV on day 8

- **No differences in adverse events up to 28 days**

![Bar chart showing treatment response and clinical success for 1-dose and 2-dose regimens.](image-url)
Single-Dose Oritavancin in the Treatment of Acute Bacterial Skin Infections (SOLO I)


Single-Dose Oritavancin Versus 7-10 Days of Vancomycin in the Treatment of Gram-Positive Acute Bacterial Skin and Skin Structure Infections (SOLO II)

Study Design and Treatment
SOLO I & SOLO II

• Design
  • International, multicenter, randomized, double-blind phase 3

• Intervention
  • Oritavancin 1200 mg IV once
  • Vancomycin 15 mg/kg IV q12h x 7-10 days

• Population
  • ≥18 years of age
  • Acute bacterial skin and skin-structure infection
    • Thought/proven gram-positive causal pathogen
    • Requiring ≥ 7 days of IV antibiotics

Efficacy and Safety Assessments
SOLO I & SOLO II

• **Primary Outcome (ECE)**
  • Cessation of spreading/reduced size of lesion
  • Absence of fever
  • No rescue antibiotic administered

• **Secondary Outcomes**
  • Clinical cure
  • ≥20% reduction in lesion size at ECE

• **Safety Outcomes**
  • Adverse events

*ECE = Early clinical evaluation (48-72 hours after drug initiation)

Primacy Outcome (non-inferiority)
SOLO I & SOLO II

Composite

% of patients

SOLO I
- Vancomycin: 79%
- Oritavancin: 82%

SOLO II
- Vancomycin: 83%
- Oritavancin: 80%

Clinical cure

% of patients

SOLO I
- Vancomycin: 80%
- Oritavancin: 81%

SOLO II
- Vancomycin: 83%
- Oritavancin: 87%

Lesion reduction ≥ 20%

% of patients

SOLO I
- Vancomycin: 85%
- Oritavancin: 86%

SOLO II
- Vancomycin: 87%
- Oritavancin: 86%

Microbiological Population

SOLO I & SOLO II

At least one pathogen

Staphylococcus aureus

MRSA

MSSA

Streptococcus species

S. anginosus group

S. pyogenes

Difference

MRSA = Methicillin-Resistant S. aureus
MSSA = Methicillin-Sensitive S. aureus

Vancomycin better
Oritavancin better

Study Critique
SOLO I & SOLO II

• Strengths
  • Study design
  • Many subgroup analyses & confounder assessments
  • Consistent baseline characteristics
  • Extended surveillance of adverse events

• Limitations
  • High drop out rates
  • Unnecessary broad MRSA coverage
  • No de-escalation with oritavancin
  • “Clinical cure” as assessed by the investigator

Safety

• Possibly more serious anaphylactic reactions
• Dalbavancin
  • Hypotension in phase 2 studies
• Oritavancin
  • Infusion-related reactions
  • Osteomyelitis
  • Coagulation test abnormalities

Question 2

• 34 y/o M POD 8 s/p Whipple’s procedure is re-admitted for acute pulmonary embolism started on high intensity heparin infusion. He is also septic and there is concern for anastomotic leak. His surgical site appears dirty and is draining purulent fluid that is culture-confirmed MRSA. Which antibiotic(s) would you begin?
  • Dalbavancin
  • Oritavancin
  • Vancomycin + piperacillin/tazobactam
  • Levofloxacin + gentamicin
Dalbavancin and Oritavancin

Outside of Acute Bacterial Skin and Skin Structure Infections
Dalbavancin
Catheter-Related Bloodstream Infection

Open-label, randomized, controlled, phase 2 trial

Adults with signs of bacteremia possibly/definitely associated with a catheter

Dalbavancin 1000mg IV day 1 then 500mg IV day 8
Vancomycin 1000mg IV q12h

CoNS
MSSA
MRSA
E. faecalis

Success at Test-of-Cure Visit

% of patients

Overall Clinical Microbiological

Vancomycin Dalbavancin


MRSA = Methicillin-Resistant S. aureus
MSSA = Methicillin-Sensitive S. aureus
CoNS = Coagulase-negative Staphylococcus
Dalbavancin
Bone and Articular Tissue Infection

• Pharmacokinetic modeling of two Phase I studies

<table>
<thead>
<tr>
<th></th>
<th>Day 14 Concentrations</th>
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<tbody>
<tr>
<td>Plasma*</td>
<td>15.3</td>
</tr>
<tr>
<td>Synovium†</td>
<td>15.9</td>
</tr>
<tr>
<td>Synovial fluid*</td>
<td>6.2</td>
</tr>
<tr>
<td>Bone†</td>
<td>4.1</td>
</tr>
<tr>
<td>Skin†</td>
<td>13.8</td>
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</table>

*mcg/mL
†mcg/g

Dalbavancin
Activity against *Staphylococcal* biofilms

- Minimum biofilm inhibitory concentration (MBIC)
- Minimum biofilm bactericidal concentration (MBBC)

<table>
<thead>
<tr>
<th></th>
<th>Dalbavancin</th>
<th></th>
<th></th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>MBIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>MBIC&lt;sub&gt;90&lt;/sub&gt;</td>
</tr>
<tr>
<td>MRSA</td>
<td>0.03</td>
<td>0.06</td>
<td>0.06</td>
<td>0.25</td>
</tr>
<tr>
<td>MSSA</td>
<td>0.03</td>
<td>0.06</td>
<td>0.06</td>
<td>0.12</td>
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<tr>
<td>MRSE</td>
<td>0.03</td>
<td>0.12</td>
<td>0.06</td>
<td>0.50</td>
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<tr>
<td>MSSE</td>
<td>0.03</td>
<td>0.12</td>
<td>0.03</td>
<td>0.25</td>
</tr>
</tbody>
</table>

MRSE = Methicillin-resistant *S. epidermidis*
MSSE = Methicillin-sensitive *S. epidermidis*
MIC = Minimum inhibitory concentration

**Oritavancin**  
**Blood Stream Infection**

- **Two exploratory phase 2 multicenter, open-label, uncontrolled studies**

- **Dose escalation in gram-positive bacteremia q24h for 7-10 days**
  - 3 mg/kg then 2 mg/kg/day
  - 4 mg/kg then 3 mg/kg/day
  - 5 mg/kg then 4 mg/kg/day

- **Dose finding in subjects with S. aureus bacteremia q24h for 10-14 days**
  - 5 mg/kg/day
  - 6.5 mg/kg/day
  - 8 mg/kg/day
  - 10 mg/kg/day

- **9/10 complete eradication of gram-positive pathogens from blood cultures**
- **No serious adverse effects**

<table>
<thead>
<tr>
<th>Dose (mg/kg/day)</th>
<th>Composite Outcome Success</th>
<th>Clinical Cure</th>
<th>Bacteriologic Eradication</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (n=6)</td>
<td>5 (83%)</td>
<td>5 (83%)</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>6.5 (n=7)</td>
<td>5 (71%)</td>
<td>5 (71%)</td>
<td>6 (86%)</td>
</tr>
<tr>
<td>8 (n=24)</td>
<td>16 (67%)</td>
<td>17 (71%)</td>
<td>19 (79%)</td>
</tr>
<tr>
<td>10 (n=20)</td>
<td>16 (80%)</td>
<td>16 (80%)</td>
<td>17 (85%)</td>
</tr>
<tr>
<td>Comparator (n=27)</td>
<td>19 (70%)</td>
<td>20 (74%)</td>
<td>21 (78%)</td>
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</tbody>
</table>

Information provided by The Medicines Company for Healthcare Professionals only. V01-11-0116
**Oritavancin**

78 y/o M w/ bioprosthetic aortic valve endocarditis

*Enterococcus faecium* (Vancomycin-resistant)

Daptomycin 8 mg/kg

8 weeks in, re-admitted CVC infection
Oral linezolid x 2 weeks

Bacteremia recurred @ 48 hours
Tigecycline added

5 months later VRE bacteremia
Daptomycin + tigecycline

Bacteremia recurred @ 72 hours
(Daptomycin-resistant)

Linezolid + tigecycline

Anorexia, nausea, ↑lactate, ↓platelets

Oritavancin 1200mg weekly

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Initial</th>
<th>Antibiotic</th>
<th>Initial</th>
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<tbody>
<tr>
<td>Ampicillin</td>
<td>6 (R)*</td>
<td>Daptomycin</td>
<td>4 (S)†</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>6 (R)*</td>
<td>Quinupristin/</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dalfopristin</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>6 (R)*</td>
<td>Tigecycline</td>
<td>0.25†</td>
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<td></td>
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<tr>
<td>Linezolid</td>
<td>30 (S)*</td>
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<table>
<thead>
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<tr>
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<td><strong>Daptomycin</strong></td>
<td>6 (R)†</td>
</tr>
<tr>
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<td>6 (R)*</td>
<td>Quinupristin/</td>
<td>1.5 (I)†</td>
</tr>
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<td>dalfopristin</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>6 (R)*</td>
<td>Tigecycline</td>
<td>0.25†</td>
</tr>
<tr>
<td>Telavancin</td>
<td>0.19†</td>
<td>Oritavancin</td>
<td>0.5†</td>
</tr>
<tr>
<td>Linezolid</td>
<td>31 (S)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Kirby Bauer disk diffusion (mm)
†Minimum inhibitory concentration (mcg/mL)

VRE = Vancomycin-resistant *Enterococcus*
CVC = Central venous catheter

Oritavancin
78 y/o M w/ bioprosthetic aortic valve

Completed 7 weeks of Oritavancin

8 days later VRE bacteremia
Oritavancin 1200mg twice weekly

Bacteremia recurred @ 2 weeks
AVR/MVR + Linezolid + Tigecycline

10 weeks later LFT abnormalities
Oritavancin stopped

Post-operatively anorexia, nausea, ↑lactate
Oritavancin 1200mg twice weekly

7 months: LFTs returned normal
17 months: blood cultures clear

<table>
<thead>
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<th>8 mo.</th>
<th>Antibiotic</th>
<th>8 mo.</th>
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<tbody>
<tr>
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<td>6 (R)*</td>
<td>Daptomycin</td>
<td>4 (S)†</td>
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<tr>
<td>Vancomycin</td>
<td>6 (R)*</td>
<td>Quinupristin/</td>
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</tr>
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<td>dalfopristin</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>6 (R)*</td>
<td>Tigecycline</td>
<td>0.094†</td>
</tr>
<tr>
<td>Telavancin</td>
<td>32†</td>
<td>Oritavancin</td>
<td>0.5†</td>
</tr>
<tr>
<td>Linezolid</td>
<td>35 (R)*</td>
<td></td>
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</tbody>
</table>

Test                                      Value
Alanine aminotransferase                  84 U/L
Aspartate aminotransferase                77 U/L
Alkaline phosphatase                      333 U/L

*Kirby Bauer disk diffusion (mm)
†Minimum inhibitory concentration (mcg/mL)
AVR = aortic valve replacement
MVR = mitral valve replacement
VRE = Vancomycin-resistant Enterococcus
LFT = Liver function test

Antimicrobial Stewardship Considerations

- Streamlining therapy
- Potential overuse
- Hypersensitivity reactions
- Avoidance of costly inpatient stays and CVC placement for long-term antibiotics
- High acquisition cost

CVC = Central venous catheter
Vancomycin
1500mg q12h
x 14 days
$121.80

Dalbavancin
1500mg
$4,176

Oritavancin
1200mg
$3,704

NON-FORMULARY
NON-ORDERABLE
Ongoing Clinical Trials

• Dalbavancin
  • Safety and efficacy in adults with osteomyelitis
  • Adults with community-acquired bacterial pneumonia*
  • Children with ABSSSI, osteomyelitis

• Oritavancin
  • PK and safety of co-administration with warfarin
  • Safety in children with bacterial infections

*Withdrawn prior to enrollment

https://clinicaltrials.gov/ct2/show/NCT02685033
https://clinicaltrials.gov/ct2/show/NCT02269644
https://clinicaltrials.gov/ct2/show/NCT02814916
https://clinicaltrials.gov/ct2/show/NCT02134301
https://clinicaltrials.gov/ct2/show/NCT02340988
Question 3

• In the event a patient experiences anaphylaxis to oritavancin, he/she should be emergently taken to dialysis
  • True
  • False
Conclusion

• Dalbavancin and oritavancin are novel lipoglycopeptides with ultra-long half-lives allowing them to be given in a single dose with similar efficacy in ABSSSIIs compared to vancomycin.

• Dalbavancin and oritavancin have the potential to reduce costly inpatient hospital stays in patients requiring intravenous antibiotics.

• Though non-formulary at Mayo Clinic, dalbavancin and oritavancin are currently being explored for use against resistant gram positive organisms and more severe infections such as endocarditis and osteomyelitis.
Questions & Discussion