Case Presentation 4
Dalbavancin use in osteomyelitis

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Financial Declaration

I have previously received payment to deliver educational presentations from Correvio
Summary

• Review a complex case of diabetic foot osteomyelitis

• Consider relative merit of treatment options

• Consider the role of extending interval antibiotics in facilitating out-patient management of deep seated infection
Introduction

• There have never been more options for the out-patient management of osteomyelitis:
  • Traditional OPAT approaches with once daily beta-lactams or glycopeptides (ceftriaxone, ertapenem, teicoplanin)
  • Continuous infusion via elastomeric devices (flucloxacillin, piperacillin/tazobactam)
  • Highly bioavailable oral regimens, particularly in the light of the OVIVA study
  • Long acting glycopeptides (dalbavancin, oritavancin)
• How should we select between these approaches
• What role is there for newer therapies?
Case Presentation

• 54 year old man with type 2 diabetes and end organ damage

• Previous episodes of diabetic foot infection managed with oral antibiotics:
  • Short course antibiotic treatment in community and via podiatry
  • Flucloxacillin, co-amoxiclav, clindamycin and doxycycline

• Attending the diabetic foot clinic weekly with deep ulcer overlying the 5th metatarsal head
Case Presentation

• Attends the diabetic foot clinic feeling unwell

“\textit{I’ve been vomiting all weekend and shivering uncontrollably.}”

• Deterioration in the appearances of the ulcer with purulent discharge onto the dressing. Fragments of bone easily extracted from base of ulcer with strong clinical suspicion of osteomyelitis

• WCC 15, CRP 197, U&Es, LfTs normal
Case Presentation

- Admitted to hospital and started on IV flucloxacillin
- Plain film demonstrates frank destruction of 5th metatarsal shaft and deterioration of 4th and 5th MTPJ
- Blood cultures negative
- Culture of bone:
  - MSSA: Resistant to clindamycin, doxycycline
  - MRSA: Resistant to clindamycin, ciprofloxacin, trimethoprim
  - Klebsiella pneumonia: sensitive to co-amoxiclav and ciprofloxacin
  - Citrobacter freundii: sensitive to temocillin and ciprofloxacin
What would you do?
Case Presentation

• In patient therapy changed to IV vancomycin (trough 18), temocillin 2g bd and metronidazole 500mg tds

• Ongoing input from podiatry and vascular surgery

• Offered debridement ± forefoot amputation but patient refused and keen to persist with antibiotic therapy

• Clinical improvement with treatment and patient ambulant in orthotic footwear
OPAT Referral

- Options considered for discharge:
  - Daily teicoplanin with ciprofloxacin
    - Patient not willing to self-administer or attend hospital daily
    - Home IV antibiotics not available in our area
  - 3x/wk teicoplanin* with ciprofloxacin
    - Patient willing to attend hospital 3x/wk in hospital transport
    - Excellent renal function (eGFR 92 on Cockcroft/Gault) so high risk for subtherapeutic dosing
  - Linezolid with ciprofloxacin
    - Suprisingly, no significant drug interactions limiting therapy
    - On metformin – no strong evidence of increased risk of lactaemia

* Lamont et al, JAC 2009
OPAT Management

• Discharged after 8 days in hospital on linezolid 600mg bd and ciprofloxacin 750mg bd with plan for weekly review in OPAT for toxicity monitoring and weekly review in MDT foot clinic

• Given quinolone information sheet regarding tendonopathy and other severe quinolone adverse effects*

• Seen after 72 hours to repeat ECG:
  • No evidence of QT prolongation

* MHRA 2019
OPAT Management

• Attends OPAT after 7 days of linezolid:
  • Nausea and lethargy
  • No change in FBC
  • Lactate 5.6 mmol/l

• Linezolid discontinued and loaded with teicoplanin over 3 days
• Ciprofloxacin continued
OPAT Management

• Attends OPAT 3x/week for teicoplanin
• Problems with difficult pharmacokinetics:
  • Low trough levels despite maximal dosing (2g 3x/wk)
  • Patient experiencing post-infusion shivering and somnolence
• CRP rises from 53 to 157 over subsequent 2 weeks

• Patient remains well in between infusions and does not wish readmission to hospital
• Patients with high eGFRs are frequently underdosed by extended interval teicoplanin dosing strategies.

• Frequently not possible to achieve therapeutic troughs without infusion related toxicity.

Fiona Robb, unpublished data.
Options considered:

- Revisiting self-administration of teicoplanin daily to achieve appropriate levels
  - Patient is clear that he would not wish to attempt self-administration and could not attend OPAT daily
- Readmission to hospital to facilitate therapy with vancomycin
  - Patient aware that this remains an option. Wishes to avoid admission if possible.
- Reattempting oral treatment with tedizolid
  - Some data supporting use in patients with previous linezolid toxicity
- Switching to IV dalbavancin
  - Longer half-life facilitates extended interval dosing
  - Limited data in management of osteomyelitis
OPAT Management

• Dalbavancin treatment selected

• Patient given 1g loading dose and then 500mg weekly to complete 6 weeks
  • Ciprofloxacin continued throughout

• Good clinical response with CRP falling to <20 over period of treatment
  • No further antibiotics at 4 months follow up after stopping dalbavancin
Dalbavancin

- Novel lipoglycopeptide antibiotic
- Administered by intravenous infusion over 30 minutes
- Highly active against Gram positive bacteria with similar spectrum to vancomycin
- Principle therapeutic advantage is prolonged half-life permitting once weekly dosing
- Patients receive either 1500mg as a single dose or 1000mg at baseline and then 500mg one week later
## Dalbavancin

### Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Dalbavancin</th>
<th>Vancomycin/Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Cure at 7 days</td>
<td>80%</td>
<td>70%</td>
</tr>
</tbody>
</table>

### Adverse Effects

<table>
<thead>
<tr>
<th></th>
<th>Dalbavancin</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2.5%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0.8%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Pruritis</td>
<td>0.6%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Rash</td>
<td>1.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.7%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Headache</td>
<td>3.8%</td>
<td>3.5%</td>
</tr>
<tr>
<td>ALT increased</td>
<td>1.2%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0.6%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

Boucher et al, NEJM 2014
## Antimicrobial Activity

<table>
<thead>
<tr>
<th>Organism (No. tested)</th>
<th>MIC, µg/mL</th>
<th>% inhibited at dalbavancin MIC, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50%</td>
<td>90%</td>
</tr>
<tr>
<td><em>S. aureus</em> (2861)</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>MSSA (2203)</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>MRSA (658)</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>Vancomycin MIC ≤ 1 mg/L (642)</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>Vancomycin MIC 2 mg/L (16)</td>
<td>0.06</td>
<td>0.12</td>
</tr>
<tr>
<td>VGS a (69)</td>
<td>≤0.03</td>
<td>≤0.03</td>
</tr>
<tr>
<td><em>S. anginosus</em> group (48)</td>
<td>≤0.03</td>
<td>≤0.03</td>
</tr>
<tr>
<td>BHS b (466)</td>
<td>≤0.03</td>
<td>≤0.03</td>
</tr>
<tr>
<td><em>S. pyogenes</em> (223)</td>
<td>≤0.03</td>
<td>≤0.03</td>
</tr>
<tr>
<td><em>S. agalactiae</em> (135)</td>
<td>≤0.03</td>
<td>0.06</td>
</tr>
<tr>
<td><em>S. dysgalactiae</em> (47)</td>
<td>≤0.03</td>
<td>≤0.03</td>
</tr>
</tbody>
</table>

Mendez et al, JAC 2016
Rappo et al

• Randomised controlled trial in long bone osteomyelitis.

• Patients randomized in 7:1 ratio to:
  • 1.5g dalbavancin on day 1 and 8
  • Standard care (investigator determined antibiotics)
1.5gx2 Dalbavancin Dosing

Dunne et al, AAC, 2015
Rappo et al

- 100% of patients had debridement at time of randomization
- Staphylococcus aureus isolated in 60% of patients (3% bacteraemic)
  - 5/48 patients with Staph aureus had MRSA
- 13 patients had mixed Gm +ve/Gm –ve infection and received concomitant IV antibiotics (aztreonam)
- 2 patients in dalbavancin group excluded as only Gram negatives isolated
### Table 2. Hospital Stay and Antibiotic Treatment (mITT Population)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dalbavancin (n = 67)</th>
<th>Standard of Care (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of hospital stay, d</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>15.8 ± 7.1</td>
<td>33.3 ± 14.2</td>
</tr>
<tr>
<td>Median (range)</td>
<td>15.0 (8–38)</td>
<td>30.5 (11–56)</td>
</tr>
<tr>
<td><strong>Days of IV antibiotic treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.0 ± 0</td>
<td>31.6 ± 7.0</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2 (2–2)</td>
<td>29 (29–49)</td>
</tr>
<tr>
<td><strong>Total IV infusion duration, h</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.0 ± 0.02</td>
<td>101.3 ± 20.8</td>
</tr>
<tr>
<td>Median (range)</td>
<td>1.0 (1.0–1.1)</td>
<td>112.6 (66.9–113.3)</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; mITT, modified intent-to-treat.
Rappo et al

- No significant safety concerns – 1 non-severe drug related AE
Dalbavancin use in Glasgow

- Targeted on patients unable to be managed by Glasgow’s traditional OPAT model
  - People who inject drugs
  - Unstable social circumstances
  - Patients with cognitive impairment
  - Elderly patients with multiple comorbidities
- Used only where other strategies, including oral strategies are not suitable

<table>
<thead>
<tr>
<th>Dalbavancin Reason</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWID/Substance misuse</td>
<td>16 (24%)</td>
</tr>
<tr>
<td>Mobility/transport</td>
<td>31 (46%)</td>
</tr>
<tr>
<td>IV access</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Drug allergy/intolerance</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Psychiatric comorbidity/dementia</td>
<td>11 (16%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>N (%)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Skin/soft tissue infection</td>
<td>23 (34%)</td>
</tr>
<tr>
<td>Staph. aureus bacteraemia</td>
<td>9 (13%)</td>
</tr>
<tr>
<td>Endocarditis (Left/Right sided)</td>
<td>7/2 (13%)</td>
</tr>
<tr>
<td>Line infection</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Native osteomyelitis/septic arthritis</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>Spinal infection</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Prosthetic joint infection</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Other orthopaedic metalwork infection</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>
Adverse Outcomes

Drug Adverse Effects
• 118 doses administered to 67 patients (median 1, range 1-6)
• 2 possible adverse reactions:
  • Both rash
  • Both probably not caused by dalbavancin (1 clindamycin, 1 rifampicin)
• 1 definite:
  • Teicoplanin-like reaction

OPAT Failures
• 3 patients with soft tissue infection readmitted within 30 days
• 1 patient readmitted with UTI
• 2 therapeutic failures:
  • 1 patient with vascular graft infection being managed palliatively
  • 1 patient with chronically infected knee replacement not suitable for surgery
Dalbavancin Dosing

• No clear consensus on appropriate prolonged dosing
• Very wide range of dalbavancin dosing reported in the literature:
  • 1000mg + 500mg weekly
  • 1000mg fortnightly
  • 1500mg x2 a week apart
  • 1500mg fortnightly
  • 1500mg + 1000mg fortnightly
  • 1000mg weekly
• Therapeutic drug monitoring not widely available
There are many strategies to support patients with complex Gram +ve infections in the community. The majority can be successfully managed with oral/traditional OPAT strategies. There are many reasons that patients may be unsuitable for such approaches and these patients have often remained in hospital for prolonged periods. Dalbavancin represents a potential treatment option where other strategies are unsuitable.