Telavancin for the treatment of methicillin-resistant Staphylococcus aureus osteomyelitis

Jennifer D. Twilla1,2, Michael S. Gelfand1,3*, Kerry O. Cleveland1,3* and Justin B. Usery1,2

1Methodist University Hospital, Memphis, TN, USA; 2Department of Clinical Pharmacy, University of Tennessee Health Science Center, Memphis, TN, USA; 3Department of Medicine, Division of Infectious Diseases, University of Tennessee Health Science Center, Memphis, TN, USA

*Corresponding author. Tel: +1-901-448-5770; Fax: +1-901-448-5940; E-mail: kcleveland@uthsc.edu

Keywords: vancomycin, linezolid, daptomycin, tigecycline, lipoglycopeptide

Sir,

With a rapid increase in invasive infections caused by methicillin-resistant Staphylococcus aureus (MRSA), there is a demand for antimicrobials with enhanced activity against MRSA. The concentration-dependent, bactericidal lipoglycopeptide telavancin was approved in 2009 for treatment of complicated skin and skin-structure infections due to susceptible organisms. The emergence of glycopeptide resistance and clinical failures of vancomycin therapy in invasive MRSA infections, including osteomyelitis, has led to the unlabelled use of alternatives to vancomycin for treatment of these infections. We report four patients with MRSA osteomyelitis who failed standard vancomycin therapy and were successfully retreated with telavancin and surgical intervention.

A patient was admitted with inability to ambulate for 1 day. This was preceded by a 4 day history of progressive leg weakness and a 2 month history of lower back pain. There also was a history of multiple carbuncles of the face, neck and buttocks, but no antimicrobial therapy had been administered for these. No fever was present. White blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated. Magnetic resonance imaging (MRI) revealed T4–7 vertebral osteomyelitis as well as T5–6 discitis with an anterior epidural phlegmon and stenosis with spinal cord compression.

CT revealed a 2 cm mass in the left upper lung and a large right hip effusion. MRI was consistent with right hip septic arthritis and osteomyelitis of the right acetabulum, femoral head, femoral neck and lesser trochanter. Blood cultures grew MRSA (vancomycin MIC 1 mg/L, linezolid MIC 1 mg/L and daptomycin MIC ≤0.5 mg/L). Telavancin 10 mg/kg iv daily was begun. While receiving 10 weeks of telavancin therapy, there was resolution of fever and leucocytosis and normalization of ESR and CRP values. Gradual recovery of leg strength and ability to ambulate was noted. There was no evidence of recurrent infection 4 months after completion of telavancin.

A patient with the sudden onset of leg weakness and urinary incontinence was transferred from another hospital after a lengthy hospitalization with MRSA bacteraemia (vancomycin MIC 1 mg/L, linezolid MIC 2 mg/L and daptomycin MIC ≤0.5 mg/L) from cellulitis complicated by sepsis, respiratory failure with pneumonia, renal dysfunction and hepatic encephalopathy. Despite sequential treatment with adequate doses of vancomycin (14 days), linezolid (7 days) and daptomycin (14 days), the MRSA bacteraemia persisted with unchanged MIC values.

Fever was absent. WBC, ESR and CRP values were elevated. Transthoracic echocardiography and transoesophageal echocardiography (TOE) did not reveal valvular vegetations. MRI showed an epidural abscess extending from T6 to L2, L1 vertebral osteomyelitis and a left psoas abscess. Telavancin 10 mg/kg iv daily was begun.

T6–7 decompressive laminectomy was performed and the abscess was evacuated. Cultures of the blood and abscess grew MRSA with unchanged MIC values of vancomycin, linezolid and daptomycin. Telavancin MIC was 0.25 mg/L.

Telavancin was administered for 8 weeks with improvement in leg weakness and urinary incontinence. There was no evidence of recurrence 7 months after completion of telavancin.

A patient presented with a 1 week history of right hip pain after a fall. Fever and leucocytosis were present. There was a remote history of a gunshot wound to the right hip.

CT revealed a 2 cm mass in the left upper lung and a large right hip effusion. MRI was consistent with right hip septic arthritis and osteomyelitis of the right acetabulum, femoral head, femoral neck and lesser trochanter. Blood cultures grew MRSA (vancomycin MIC 1 mg/L, linezolid MIC 1 mg/L and daptomycin MIC ≤0.5 mg/L). Ceftazi-done 2 g iv daily and vancomycin 13 mg/kg iv every 12 h were begun and continued for 5 days.

Telavancin for the treatment of methicillin-resistant Staphylococcus aureus osteomyelitis

J Antimicrob Chemother 2011
doi:10.1093/jac/dkr329
Advance Access publication 10 August 2011

A Girdlestone procedure with irrigation and debridement of the right hip was performed. Histopathology was consistent with chronic osteomyelitis. Therapy was changed to daptomycin 6 mg/kg iv daily. Despite 12 days of daptomycin treatment, fever and leukocytosis persisted. Culture of purulent drainage from a surgical drain grew MRSA (MIC values were unchanged).

Repeat CT showed development of a 1.5 cm cavitory lesion in the left lung base and a persistent 2 cm mass in the left upper lung. Multiloculated air/fluid collections were noted in the right iliopectas consistent with abscess. No valvular vegetations were seen on TOE. Therapy was changed to telavancin 10 mg/kg iv daily. Culture of material from the right iliopectas abscess obtained by CT-guided drainage grew MRSA with an MIC of telavancin of 0.25 mg/L. Other MIC values were identical to those previously reported.

While completing a 6 week course of telavancin, the fever, leukocytosis and purulent drainage resolved. The pulmonary lesion was noted on repeat CT to have resolved after treatment. No evidence of recurrent infection was noted 6 months after completion of telavancin.

A patient was admitted on transfer with a paraparesis of the legs, which occurred after progressive weakness and urinary and faecal incontinence. During the antecedent 5 month hospitalization, the patient had experienced four episodes of MRSA bacteremia with initial MIC values of 2 mg/L for vancomycin, 2 mg/L for linezolid and 0.5 mg/L for daptomycin, and had received four 14 day courses of iv vancomycin with therapeutic trough levels. On the fourth recurrence of MRSA bacteremia, the daptomycin MIC was noted to have increased to 4 mg/L, but the vancomycin MIC value was unchanged.

On admission no fever was present. Blood cultures were negative, but ESR and CRP were elevated. TOE showed no valvular vegetations. MRI revealed discitis and osteomyelitis at T8–9 with an extensive paravertebral phlegmon and cord compromise. Laminectomy and evacuation of the abscess were performed. Culture of the abscess grew MRSA (MICs of vancomycin, linezolid and daptomycin were unchanged, and the MICs of telavancin and tetracycline were 0.25 and ≤4 mg/L, respectively).

Telavancin 10 mg/kg iv daily was begun with gradual improvement in the neurological status and normalization of the ESR and CRP. After 4 weeks, there was noted to be a rise in serum creatinine to 2.5 mg/dL and development of eosinophilia. Therapy was changed to tigecycline 50 mg iv every 12 h. Subsequent to 5 weeks of antibiotic therapy, the spine was stabilized with pedicle screws and rods. Post-operatively the patient received 2 weeks of tigecycline followed by 2 weeks of linezolid 600 mg orally twice daily, had improvement of the serum creatinine to 1.5 mg/dL and demonstrated no evidence of recurrence 1 month after completion therapy.

MRSA has become an important cause of osteomyelitis.1 Vancomycin is the standard recommended therapy, but both failure of therapy and serious side effects, including renal damage, make it a less than ideal agent.2 Penetration of vancomycin into bone may not be optimal for treatment of bone infections.3 In addition, various forms of resistance to vancomycin have emerged in MRSA.4 While not approved for treatment of osteomyelitis, daptomycin has become a popular agent because of excellent MRSA activity, convenient once daily dosing and its safety profile.5 MRSA isolates with increased daptomycin MICs have been infrequently reported after treatment with vancomycin,6 as seen in our fourth patient. Daptomycin is not indicated for treatment of pneumonia.7

Telavancin’s excellent bactericidal activity and low MIC values for MRSA isolates make it an attractive alternative to vancomycin and daptomycin for MRSA infections. It is approved for treatment of skin and soft tissue infections and has been used successfully in pneumonia.8 We are unaware of previous reports of telavancin therapy for osteomyelitis. While it is not approved for the treatment of osteomyelitis, a study in a rabbit model of MRSA osteomyelitis showed good activity of telavancin as well as linezolid and vancomycin.9 It is administered once daily and no monitoring of serum levels is required.6

Renal impairment was a relatively common side effect in pre-marketing studies of telavancin.8 Renal impairment was noted in one of our patients after several weeks of therapy, but the other three patients tolerated prolonged courses of telavancin without change in renal function.

Abscess development may prevent successful antibiotic therapy of osteomyelitis and source control through surgery may be critical for eradication of infection.

In conclusion, following failure of standard therapy for MRSA osteomyelitis, we have successfully treated four patients with prolonged telavancin administration and surgical intervention. Larger studies of telavancin for MRSA osteomyelitis, determination of bone penetration in patients and perhaps comparative studies with other agents will be needed to establish a definitive role for telavancin in the treatment of this difficult infection.

Funding
This study was carried out as part of our routine work.

Transparency declarations
M. S. G. has served on the speakers’ bureaus for Astellas, Cubist and Pfizer. K. O. C. has served on the speakers’ bureaus for Cubist and Pfizer. J. D. T. and J. B. U.: none to declare.

References
Table 1. MICs in mg/L for NDM-1-producing E. coli isolated from the patient; the second was isolated from blood 4 months after the original was isolated from a calciphylactic skin lesion

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Isolate 1 (calciphylactic lesion)</th>
<th>Isolate 2 (blood culture)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>&gt;64</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;32</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>&gt;64</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>&gt;64</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>&gt;256</td>
<td>&gt;256</td>
</tr>
<tr>
<td>Cefpirome</td>
<td>&gt;64</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>&gt;256</td>
<td>&gt;256</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>&gt;16</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Imipenem</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Meropenem</td>
<td>&gt;32</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>&gt;64</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Colistin</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>&gt;8</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>&lt;0.25</td>
<td>8</td>
</tr>
</tbody>
</table>

On admission, the lesions were clinically infected. Empirical treatment was with intravenous (iv) fluoroquinolones and benzylpenicillin, then piperacillin/tazobactam, without clinical response. Biopsy of the lesions led to a histological diagnosis of calciphylaxis. A biopsy sample was cultured on standard media, with E. coli, K. pneumoniae, methicillin-resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa identified using the BD Phoenix automated identification system (Oxford, UK). The E. coli and K. pneumoniae were resistant to meropenem (confirmed by Etest) and ertapenem, and to piperacillin, aztreonam, cefazidime and cefpodoxime. They remained susceptible to tigecycline and colistin. Accordingly, antimicrobial therapy was altered to 50 mg of tigecycline twice daily iv (after a 100 mg loading dose) and 500 mg of ciprofloxacin twice daily orally to cover the P. aeruginosa. Screening cultures from stool were negative for carbapenem-resistant Enterobacteriaceae.

The K. pneumoniae and E. coli isolates were referred to the Antibiotic Resistance Monitoring & Reference Laboratory of the HPA for MIC determination by BSAC agar dilution and molecular investigation. Both were multiresistant, with susceptibility confirmed only to tigecycline and colistin (MICs both <0.5 mg/L); PCR and sequencing confirmed the blaox-1 gene in both isolates, carried by plasmids belonging to the A/C /rep type, which gave closely similar profiles after digestion with the SacI enzyme. The 16S RNA methylase gene rmtC was also detected in both isolates by PCR, conferring resistance to all clinically used aminoglycosides.

The patient required prolonged hospitalization, interrupted only by 4 weeks at home. Four months after initial presentation, while being treated for ongoing infection of calciphylactic lesions, the patient developed fever. Blood cultures were taken and grew NDM-1-positive E. coli identical by PFGE to that isolated from the original lesions. Susceptibility to colistin remained, but...