Clinical experience with daptomycin for the treatment of patients with knee and hip periprosthetic joint infections

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Received 23 December 2011; returned 31 January 2012; revised 7 March 2012; accepted 12 March 2012

Objectives: To investigate the clinical efficacy and safety of daptomycin in the treatment of hip and knee periprosthetic joint infections (PJIs).

Methods: We completed a retrospective review of all patients in our institution (n = 20) who were treated with daptomycin for hip or knee PJI, over the 36 month period from January 2008 until December 2010.

Results: Infection types included eight cases with acute infections, nine cases of chronic infection and three cases of positive intraoperative cultures. Methicillin-resistant coagulase-negative Staphylococcus was the most frequent microorganism found in surgical cultures (40%). Our patients, on average, received daptomycin as salvage therapy at a dose of 6.6 mg/kg/day for 44.9 days. The overall success rate was 78.6% after a median follow-up period of 20 months. In the subgroup of patients with acute PJIs, treatment with daptomycin, debridement and implant retention was successful in all cases. We found two cases of severe side effects (one case of acute renal failure due to massive rhabdomyolysis and one of eosinophilic pneumonia) and two cases of asymptomatic transient creatine phosphokinase (CPK) level elevation.

Conclusions: The combination of high daptomycin doses with an adequate surgical approach could be a viable alternative in cases of difficult-to-treat Gram-positive PJIs. Due to the risk of potentially serious adverse events, serum CPK level should be closely monitored.

Keywords: arthroplasty, device-related infections, antibiotic therapy, treatment outcome, adverse reactions

Introduction

Periprosthetic joint infection (PJI) is a devastating complication associated with significant morbidity and healthcare utilization costs.¹,² The pathogenesis of PJI is influenced by microorganisms adhering to each other to form a biofilm. Biofilms are resistant to even high levels of many antimicrobial agents,² increasing the difficulty and cost of successful treatment. Once established, mature biofilm infections require removal of the prosthesis to achieve a cure.¹–³ The classification of PJIs is based upon the time from the index procedure, due to the probability of having an organized biofilm attach to the implant.⁴ In chronic cases, a two-stage prosthetic exchange is the most frequently selected approach; in acute cases, urgent debridement with exchange of mobile parts and prosthesis retention is an accepted treatment alternative.¹–³

In either type of case, it is of paramount importance to combine adequate surgical and antibiotic therapy.

The most common microorganisms involved in PJI are Gram-positive cocci. However, the increased incidence of PJIs due to multidrug-resistant (MDR) Gram-positive cocci is a matter of concern.⁵–⁸ In clinical practice, patients with PJI due to Gram-positive cocci are often treated with vancomycin. Heteroresistance to vancomycin, high failure rates in methicillin-resistant Staphylococcus aureus (MRSA) infections and its poor bone penetration are limitations to successful therapy with this drug.⁹ A novel cyclic lipopeptide, daptomycin, has demonstrated in vitro bactericidal activity (which does not seem to be related to an inoculum effect) against antibiotic-resistant Gram-positive bacteria—⁵,⁷,¹⁰–¹⁵ pathogens for which there are limited therapeutic alternatives. In addition, daptomycin seems to exhibit activity against the stationary-phase bacteria inside the biofilm.¹³,¹⁴ For these two reasons, daptomycin is a very attractive option in a PJI scenario.

The aim of our study is to perform a comprehensive retrospective review of our experience with daptomycin in...
Gramp-positive hip and knee PJIs, assessing its effectiveness and safety.

**Methods**

An institutional database search was performed to identify all consecutive hip or knee PJIs treated with daptomycin from January 2008 to December 2010. We retrospectively collected data for demographics, comorbidities, estimated creatinine clearance (Cockcroft–Gault formula), location of the prosthesis, type of peri-implant infection, and surgical procedures, microbiological results, duration and rationale of daptomycin treatment, adverse events and clinical outcomes.

All patients were classified following the Tsukayama system, which classifies PJIs based on the time from prosthesis implantation.

In our practice, the type of surgery performed in such cases depends upon the duration of infection and the judgement of the attending orthopaedic surgeon. Most often, in acute cases (types II and III), an urgent debridement is performed, with exchange of mobile parts and prosthesis retention, followed by prolonged antibiotic therapy (6–12 weeks). In many chronic cases (type IV), a two-stage replacement is the chosen option. In the period between the operative stages, we use a prefabricated, antibiotic-loaded cement spacer (Vancogenx, Tecres, Italy) preloaded with vancomycin and gentamicin. The second-stage reconstruction procedure is carried out after a period of specific antibiotic treatment, and after the wound has healed and the C-reactive protein has returned to normal, and if surgery is deemed medically advisable. In selected knee cases with difficult-to-treat chronic infection, joint fusion is an option. We consider that in type I cases, a single-stage exchange procedure has already been completed, and the treatment that follows consists of targeted antibiotic treatment over the next 8–12 weeks (oral) or 5–6 weeks (intravenous).

To effectively target the antibiotic treatment, five to six different samples are taken directly from bone or peri-prosthetic tissue during surgery. We consider cultures evaluable if at least two positive samples of the same microorganism are identified. A prolonged culture protocol (12–14 days) is applied, with reincubation in enrichment medium. Microorganism identifications are performed by Gram stain, colony morphology, catalase, clot-plasma and DNase in the case of staphylococci, or a physiological test in the case of streptococci. Definitive species identification is performed with standard procedures using an automatic or semi-automated system (Vitek 2 or API System from bioMérieux S.A., Marcy l’Etoile, France). Antimicrobial susceptibility is assessed by the disc diffusion method (Neo-Sensitabs™, Rosco Diagnostica A/S, Denmark) and Etest® (bioMérieux S.A.). The MICs of glycopeptides and daptomycin are assessed according to CLSI recommendations.

Daptomycin dosage and duration is established by infectious diseases specialists. In patients with advanced renal insufficiency, daptomycin is administered every 48 h.7,12

Our patients receive daptomycin as a salvage treatment: (i) when other antibiotics (glycopeptides, linezolid etc.) cannot be used due to resistance, any adverse reaction, renal failure or previous treatment failure; or (ii) empirically, in cases with PJIs due to suspected MDR Gram-positive cocci and chronic renal insufficiency. Chronic renal insufficiency is defined here as a creatine clearance value <60 mL/h.

As part of our protocol, patients’ laboratory tests are checked weekly once daptomycin treatment has begun, including serum creatine phosphokinase (CPK) levels and other blood parameters. We define asymptomatic transient elevation of serum CPK levels as CPK values above the normal range (30–150 IU/L) without any associated clinical manifestation. We define daptomycin therapy failure as a need for subsequent infection-related surgery for persistence or relapse of the infection, or the need for prolonged suppressive antibiotic treatment.16 Relapse is considered to have occurred if infection reappears after antibiotic therapy is discontinued (with the same microorganism as had been isolated in the second surgical procedure).

**Statistical analysis**

Categorical variables are expressed as percentages, and numerical data as the median and range. Cure percentages have been calculated only for patients treated with daptomycin for >50% of the course of antibiotic treatment, although all patients are included in our analysis of safety outcomes.

**Results**

A total of 20 patients were treated with daptomycin for PJIs. These included 7 males and 13 females. The median age of the daptomycin-treated patients was 81 years (range: 46–88). Five of the 20 patients had a history of chronic renal failure (Table 1).

The types of infections were as follows: eight cases were considered to have acute infections (types II and III), nine cases were considered to have chronic infections (type IV) and there were three cases with positive intraoperative cultures (type I) (Table 2).

Methicillin-resistant coagulase-negative Staphylococcus (MRCoNS) was the most frequent microorganism found in surgical cultures (40%). MRSA caused PJIs in two patients; the MICs of vancomycin were determined to be 1.5 mg/L (Patient 10) and 4 mg/L (Patient 15), respectively. The MICs of other staphylococcal species were only determined in selected cases, e.g. one case (Patient 16) of coagulase-negative Staphylococcus relapsed PJIs, for which the vancomycin MIC was 3 mg/L, the teicoplanin MIC was 4 mg/L and the daptomycin MIC was 0.094 mg/L. None of our patients previously exposed to linezolid developed resistance.

**Table 1. Patient demographic information**

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<td>M</td>
<td>71</td>
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<td>F</td>
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<td>F</td>
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<td>intolerance</td>
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<td>F</td>
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M, male; F, female; CRF, chronic renal failure.
Table 2. Characterization of patients’ infections and treatments

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<tr>
<th>Patient</th>
<th>Prosthesis type</th>
<th>Type of infection</th>
<th>Surgical procedure</th>
<th>Pathogen</th>
<th>Resistance profile</th>
<th>DAP dose (mg/kg/day)</th>
<th>DAP duration (days)</th>
<th>RIF</th>
<th>Total antibiotic (days)b</th>
<th>Total time under DAP (%)</th>
<th>Adverse effects</th>
<th>Evaluable for DAP outcome</th>
<th>Outcome</th>
<th>Follow-up (months)</th>
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<td>CLI</td>
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THA, total hip arthroplasty; TKA, total knee arthroplasty; D + PR, debridement and prosthesis retention; R + ARF, rhabdomyolysis and acute renal failure; DAP, daptomycin; RIF, rifampicin; CLI, clindamycin; LZD, linezolid; LVX, levofloxacin; SXT, trimethoprim/sulfamethoxazole; CXN, cloxacillin; GEN, gentamicin; CIP, ciprofloxacin; TET, tetracycline; ERY, erythromycin.

aTsukayama classification: type I, intraoperative positive culture; type II, acute infections; type III, haematogenous infections; and type IV, chronic infections.

bFor patients treated with an additional antibiotic, the additional antibiotic is shown in parentheses.
to this drug. The types of microorganisms involved in the infected prostheses are shown in Table 2.

**Surgical approach**

In all cases, surgical samples were obtained before beginning daptomycin therapy. Among acute PJI cases, five out of eight patients (63%) were managed with urgent debridement, exchange of mobile parts and prosthesis retention. The remaining three cases (37%) were treated with a two-stage procedure.

Chronic infections were managed with staged reconstruction. At the second stage, in five cases the selected reconstruction procedure was prosthesis revision. In four cases, knee fusion was the option chosen. The three cases with type I infection were not reoperated; we consider these ‘one-stage’ revisions (Table 2).

**Antibiotic therapy**

All patients were initially treated with daptomycin. In 8 out of 20 cases, daptomycin was chosen due to previous intolerance of vancomycin or linezolid treatment. In seven cases, the reason was previous vancomycin or linezolid failure. Five cases were treated with daptomycin because of renal failure or impaired renal function (Table 1).

Daptomycin was administered at a dose range of 4–9 mg/kg/day (Table 2). Fourteen out of the 20 cases examined were considered evaluable for the purposes of this study. The criterion used here was that the patient had been on daptomycin for ≥50% of the course of antibiotic treatment. In these 14 patients, the mean duration of daptomycin therapy was 44.9 days (range: 14–69 days). The median dosage was 6.6 mg/kg/day. The median global time under antibiotic treatment in this cohort was 57.5 days (range: 14–90 days) (Table 2).

**Outcomes**

Among the 14 patients who were evaluable for clinical efficacy, we observed three infection recurrences—at 12 months (Patient 5), 4 months (Patient 19) and 1 month (Patient 20) of follow-up—with an overall success rate of 78.6% (11 out of 14). The remaining cases were followed up for a median of 20 months (range: 12–41 months). In the three failed cases, the daptomycin dosage was 6.3 mg/kg/day on average (Table 2).

In patients with acute infections, the success rate was 83.3% (five out of six patients). Four acute infections were treated with prosthesis retention. In three of these four (Patients 4, 6 and 8), rifampicin was used in conjunction with daptomycin to treat an MRCoNS PJI. In patients treated with prosthesis retention, no relapse has been observed after 15 months of follow-up.

Among the seven patients with chronic infections, those treated with staged reconstruction had a success rate of 71.4% (five out of seven patients) at 24 months of follow-up. In just one of these cases (Patient 13), rifampicin was administered in conjunction with daptomycin.

**Daptomycin safety**

Among the 20 patients included in our study, there were two observed cases of asymptomatic transient elevation of serum CPK levels (Table 2). Neither patient had a history of renal impairment. In both cases, CPK levels rapidly normalized after daptomycin was discontinued.

We observed severe daptomycin side effects in two cases. The first case (Patient 20) was an 85-year-old woman with a history of chronic renal failure and diagnosed with a chronic methicillin-susceptible coagulase-negative Staphylococcus (MSCoNS) PJI, which was managed with knee fusion. She was treated with daptomycin at a dosage of 6 mg/kg/day. The patient developed fever and dyspnoea after 35 days of therapy, requiring admission to the intensive care unit. She presented with profound hypoxia and a chest X-ray showed extensive bilateral patchy infiltrates. Peripheral eosinophilia was detected with a peak level of 1.4×10^9/L serum eosinophils. Bronchoalveolar lavage revealed 30% eosinophils; the results of microbiological studies were negative. Daptomycin-induced eosinophilic pneumonia (EP) was suspected; daptomycin was discontinued and the patient was treated with methylprednisolone at an initial dose of 1.5 mg/kg/day, with clinical resolution.

The second case (Patient 19) was an 84-year-old woman with a chronic knee PJI and chronic renal impairment (creatinine clearance of 34 mL/min). She presented with massive rhabdomyolysis and acute renal failure. Daptomycin was prescribed, at a dosage of 8 mg/kg/day. Basal CPK levels were 29 IU/L, below the normal range of 30–150 IU/L. Eight days after daptomycin treatment was initiated, the patient was unable to lift her arms, due to severe muscle weakness. At this point, her aspartate aminotransferase was 628 IU/L, her alanine aminotransferase was 304 IU/L and her CPK level was 16391 IU/L; subsequently, daptomycin was discontinued. Afterwards, CPK levels reached a peak of 20308 IU/L. Serum creatine reached a peak value of 3.9 mg/dL. Statins were not used concomitantly in this patient. The patient required admission to the intensive care unit and transient haemodialysis. Twelve days after discontinuation of daptomycin, the patient’s liver function test and CPK levels had resolved.

**Discussion**

Daptomycin is a newer antibacterial agent, an alternative to vancomycin for the treatment of MRSA/MRCoNS infections and an attractive option for antibiotic-resistant Gram-positive PJI. Another advantage of daptomycin is its relatively long half-life, which makes it particularly suitable for outpatient administration.

Although daptomycin’s bone penetration is poor, a recent study found free bone daptomycin concentrations at steady-state to be more than the MIC<sub>90</sub> for relevant Gram-positive bacteria. However, the available data on the clinical usefulness of daptomycin in a PJI scenario are currently very limited (Table 3).

In our practice, daptomycin is currently considered a second-line drug in treating resistant Gram-positive PJI. It is an option when conventional drugs such as vancomycin cannot be used due to intolerance, allergy or renal failure, and when linezolid cannot be considered due to oral treatment intolerance or anaemia. In 7 out of 20 cases in the series presented here, daptomycin treatment was begun empirically because the patient had previous MDR Gram-positive infections where treatment with other antibiotic agents had failed.
In our experience, the overall success rate of daptomycin treatment of PJI was 78.6%. This appears similar to the 75% success rate reported by Antony et al.18 It is higher than the 54.5% success rate reported by Rao and Regalla12 in a prospective study using daptomycin (Table 3).

An inadequate dosage of daptomycin may have contributed to such difference. Rao and Regallal2 used daptomycin at a median dosage of 4 mg/kg/day. Globally, our study employed higher daptomycin doses (median of 6.6 mg/kg/day). This is a significant point because, as the published data suggest, daptomycin is safe and well tolerated at doses >6 mg/kg/day, possibly with better outcomes than at conventional doses.19–21 Another point of interest is daptomycin use in conjunction (or not) with rifampicin. This is particularly pertinent in MRSA PJI cases, among which there is a high risk of treatment failure when compared with cases of methicillin-susceptible S. aureus (MSSA) PJI. As has been described,6 recent published studies show that daptomycin at high doses is the most effective monotherapy and also that use in combination with rifampicin improves efficacy.22,23 In the four cases in our series where daptomycin was used in conjunction with rifampicin (Patients 4, 6, 8 and 13), no relapse has been observed.

In the subgroup of acute infection cases treated with daptomycin, debridement and prosthesis retention, success was observed in all four cases. Examining this group further, if we focus on the cohort of acute antibiotic-resistant Gram-positive infections, we observe no incidence of recurrent infection. Three such cases, all with MRCoNS PJI, were treated with a combination of daptomycin and rifampicin. This is especially significant because in such a subgroup of patients—i.e. with acute infection by antibiotic-resistant pathogens and treated with implant retention—the published risk of failure is as high as 84%.16,24 In these four cases, early, aggressive debridement was performed, along with exchange of the polyethylene liner. In this subgroup the mean duration of daptomycin therapy was 52 days.

Daptomycin has been well tolerated in clinical trials assessing its use, but it can occasionally cause abnormalities in liver function tests and in CPK levels.25 A few published case reports document myalgia or rhabdomyolysis and acute renal failure secondary to daptomycin use.26,27

In our short patient series, we observed two cases of very severe side effects, directly associated with daptomycin.

Regarding EP, the mechanism of daptomycin-induced pulmonary toxic effects remains unproven, but is a dramatic and potentially fatal adverse drug event if not quickly recognized and appropriately managed.28

With regard to the risk of muscle damage, three patients suffered elevations in CPK levels, one with massive rhabdomyolysis and acute renal failure. In these three patients (Patients 12, 17 and 19) the average daptomycin dosage was 6.7 mg/kg/day. Drug monitoring for daptomycin, if available, would be a very useful tool when dealing with patients under daptomycin treatment, particularly in cases on renal replacement therapy or under concomitant drugs with known associated nephrotoxicity. When drug monitoring is not available, we recommend close monitoring for symptoms of myopathy in patients treated with daptomycin, along with weekly serial follow-up of serum creatinine. If muscle weakness and/or serum creatinine elevation develops, rapid CPK assessment, liver function tests and urinalysis may be helpful in the early diagnosis of renal impairment and its management in such patients.

We recognize there are inherent weaknesses in the study presented here. First, due to its retrospective nature, the results are limited by selection biases and the lack of randomized comparative information. Second, the sample is small, making it difficult to obtain statistically significant results.

Previously available clinical data on the use of daptomycin in treating PJIs has largely been limited to short series and single-case reports. Further, reports have often concerned the treatment of periprosthetic infection concurrent with the management of osteomyelitis and osteosynthesis infections. We feel it is a strength of our study that it offers new and straightforward clinical data, reporting on a cohort of extensively followed PJI patients treated with daptomycin. Additionally, we report on two patients who experienced severe side effects—few adverse-event cases have been reported upon previously.

Conclusions
In conclusion, the combination of high daptomycin dosages and an adequate surgical approach may offer an alternative treatment modality for PJI in patients with refractory MDR Gram-positive infections, chronic renal failure or intolerance of other antimicrobial therapies. Due to the risk of potentially serious side effects, such patients should be closely followed, with periodic laboratory analysis including serum CPK.

Acknowledgements
We thank Russ Williams from Roundly Worded, for his editorial recommendations, and Nuria Guiltar Garcia, for her bibliographic support. We also want to thank Nieves Larrosa, from the Microbiology Department of our centre, for her invaluable assistance in the present study.

D. R. P. and C. P. S. belong to the Spanish Network for Research in Infectious Disease (REIPI RD 06/0008).

Funding
The study was conducted as part of the routine work of our institution.

Transparency declarations
None to declare.
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