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Daptomycin treatment in Gram-positive vascular graft infections

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ABSTRACT

Background: Daptomycin is a bactericidal antibiotic approved for the treatment of skin and soft tissue infections and right-side endocarditis. However, there is a lack of published data outlining its usefulness in vascular graft infections (VGI). The aim of this study was to describe the clinical experience of daptomycin use in the treatment of VGI caused by Gram-positive bacteria.
Methods: This was a retrospective cohort study of patients diagnosed with VGI receiving daptomycin at a tertiary care hospital during the period January 2010 to December 2012.
Results: Of a total 1066 consecutive patients who had undergone vascular grafts (VG), 25 were diagnosed with VGI. Fifteen of these patients (11 prosthetic VG, three autologous VG, one both types) received daptomycin (median dose 6.7 mg/kg/day, range 4.1–7.1 mg/kg/day; median age 69 years, range 45–83 years; 80% male). The infected bypass was removed in 13 cases. The most common reason for selecting daptomycin was kidney failure (53%). The Gram-positive organisms isolated were coagulase-negative Staphylococcus ($n = 10$), *Staphylococcus aureus* ($n = 3$) (two methicillin-resistant *S. aureus*), *Enterococcus faecium* ($n = 2$), and *Enterococcus faecalis* ($n = 1$). The mean follow-up was 69 months (interquartile range 48–72 months). Ten patients (66.7%) achieved complete healing of the VGI. A recurrence of the infection was observed in 100% of patients in whom the bypass was not removed. Among patients who did not achieve complete healing, one needed a supracondylar amputation and one died as a consequence of infection. Five patients received treatment with rifampicin in addition to daptomycin and they were all cured.
Conclusions: The use of daptomycin and surgery for Gram-positive VGI was effective and well tolerated, and this may be a good alternative for the treatment of VGI in patients with peripheral arterial disease in whom renal insufficiency is common.

Introduction

The incidence of vascular graft infections (VGI) ranges from less than 1% in abdominal vascular bypass to more than 6% in the groin area (Leroy et al., 2012; Vogel et al., 2008; Herrera et al., 2009; Hasse et al., 2013; Young et al., 2012; Seeger, 2000; Legout et al., 2012; Sousa et al., 2014). Moreover, an incision in the groin area, the existence of a surgical wound, and bacteraemia a short time before or after the surgical procedure are risk factors for VGI (Young et al., 2012; Seeger, 2000). Surgical intervention is crucial to replace the infected material and to debride the affected area (Vogel et al., 2008). The main microorganisms involved in VGI in most series are *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), coagulase-negative Staphylococcus (CoNS), and Gram-negative bacilli, particularly *Escherichia coli* and *Pseudomonas aeruginosa* (Leroy et al., 2012; Young et al., 2012; Sousa et al., 2014; Sakaguchi et al., 2008; Cowie et al., 2005).

Vancomycin has traditionally been used as a first-choice empirical treatment for VGI caused by Gram-positive microorganisms (Sousa et al., 2014; Sakaguchi et al., 2008; Cowie et al., 2005). However, its effectiveness is reduced against strains of

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S. aureus or CoNS with a minimum inhibitory concentration (MIC) ≥2 mg/l or with heteroresistance, resulting in high rates of treatment failure (Diaz et al., 2017). This fact, added to the poor penetration into prosthetic materials and nephrotoxicity of vancomycin, has encouraged the development of different therapeutic alternatives. Among them, daptomycin appears to be particularly useful, due to its bactericidal activity, its ability to penetrate into biofilms, and its synergism in association with rifampicin (Smith et al., 2009; Parra-Ruiz et al., 2010; Sader et al., 2015; Barberán and Fariñas, 2012). Due to its good tolerability and absence of renal side effects (Smith et al., 2009; Parra-Ruiz et al., 2010; Sader et al., 2015; Barberán and Fariñas, 2012; Garrigós et al., 2010), this antibiotic may be a good alternative for the treatment of VGI in elderly patients with peripheral arterial disease and functional limitations (Smith et al., 2009; Parra-Ruiz et al., 2010; Sader et al., 2015; Barberán and Fariñas, 2012; Garrigós et al., 2010; Baltch et al., 2008; Álvarez-Lerma and Gracia-Arnillas, 2010; Tally et al., 1999).

Data on the clinical outcomes of patients with VGI treated with daptomycin are scarce; only data for the prevention of VGI with daptomycin exist (Bisdas et al., 2012). Furthermore, the effect of daptomycin pre-treatment of vascular graft prostheses (VGP) for the prevention of VGI has only been investigated in vitro (Kuehn et al., 2010; Cirioni et al., 2010). These experiments do not allow researchers to draw conclusions regarding the treatment of VGI patients in clinical practice. The aim of this study was to describe the clinical experience of daptomycin use in the treatment of VGI caused by Gram-positive bacteria.

Methods

This was a retrospective cohort study of patients treated at a tertiary care university hospital during the period January 2010 to December 2012. Patients who had undergone peripheral revascularization surgery with a vascular graft (VG) and who developed an infection of the bypass that was treated with daptomycin for at least 7 days were included. Patients younger than 18 years old or with a severe immunodeficiency (haematological neoplasia, transplantation, HIV infection, or congenital immunodeficiency) were excluded. The mean follow-up was 69 months (interquartile range 48–72 months).

The criteria employed for the diagnosis of VGI were those published by Lyons et al. (2016). Data were collected on an electronic form designed specifically for this purpose and included the following: demographics, prior medical history, comorbidies (Charlson et al., 1987), analytical data on admission, clinical data of infection, surgery and post-surgical procedures, microbiology, antimicrobial treatment, and outcome. The definitions of infection and cure for VGI have been described previously (Fariñas et al., 2018).

The dose and duration of daptomycin treatment (with or without rifampicin treatment) was decided by the patient's infectious disease physician. For patients with a creatinine clearance of <30 ml/min, daptomycin was administered every 48 h.

Statistical analysis

The mean and standard deviation values were calculated for quantitative variables, whereas qualitative variables were summarized as frequencies and percentages. Each variable was studied to evaluate its parametric or non-parametric distribution with the Kolmogorov–Smirnov formula. The Student *t*-test or Mann–Whitney test was used to detect the differences between two quantitative variables; the Chi-square test was used to detect differences between two qualitative variables. The statistical analyses were performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

A total of 1066 patients underwent revascularization at the Cardiovascular Surgery Service of Marques de Valdecilla University Hospital, a tertiary level hospital, during the period January 2010 to December 2012 (2010, *n* = 376; 2011, *n* = 341; 2012, *n* = 349). Among these patients, 72 (6.8%) developed a surgical site infection and 25 (2,3%) had a VGI. Fifteen of these 25 patients (60%) diagnosed with VGI were treated with daptomycin (11 prosthetic VG, three autologous VG, one prosthetic plus autologous VG); these patients comprised the study group.

The mean age of the study patients was 69 years (45–83 years) and 80% were male (Table 1). All patients received antibiotic prophylaxis prior to surgery, 12 with cefazolin and three with vancomycin. Patient comorbidities were as follows: three had diabetes mellitus, eight had renal failure, four had chronic obstructive pulmonary disease (COPD), three had acute myocardial infarction, three had heart failure, three had stroke, and three had a peptic ulcer. With regard to the location, the surgical wound was abdominal in 33% (5/15) of the patients, left inguinal in 20% (3/15), right inguinal in 13% (2/15), right lower extremity in 20% (3/15), and left lower extremity in 13% (2/15).

The most common presenting signs and symptoms of VGI were local pain (*n* = 13), inflammatory signs of the surgical wound (*n* = 7), purulent exudate from the wound (*n* = 7), fistulous tract (*n* = 3), and fever (*n* = 3). All patients met at least one major criterion plus other criteria (major or minor) according to the proposed definitions of VGI by Lyons et al. (Table 1) (Lyons et al., 2016). All serum inflammatory markers were elevated: the erythrocyte sedimentation rate (ESR) was increased in 90% of patients (mean 49.9 mm/h, range 17–92 mm/h) and C-reactive protein (CRP) was elevated in all of the study patients (mean 9.52 mg/dl, range 1.4–31 mg/dl).

The most frequently isolated Gram-positive microorganisms were CoNS in 10 patients, followed by *S. aureus* in three (two MRSA), *Enterococcus faecium* in one, and *Enterococcus faecalis* plus *E. faecium* in one patient (Table 2).

Treatment

The bypass was removed in all but two patients. Daptomycin was administered initially as empirical therapy in 73.3% (11/15) of the cases, with the most frequently associated antibiotics being rifampicin (in five patients) and piperacillin–tazobactam (in four patients). All patients receiving rifampicin showed remission of the infection. However, only 50% (5/10) of the patients who had not received rifampicin presented total remission of the infection ($p = 0.053$). The most common reason for selecting daptomycin was the presence of renal failure (8/15 cases, 53%). The median dose of daptomycin was 6.7 mg/kg/day (range 4.7–7.14 mg/kg/day), and the mean duration of treatment with this antibiotic was 15.5 days (range 7–38 days). The only patient who had positive blood cultures died 7 days after admission and he only received 1 week of treatment with daptomycin. Thirteen patients received oral antibiotics; the mean duration of total antibiotic treatment was 31.3 days (range 7–56 days). Seven patients received levofloxacin and rifampicin, five linezolid, and one clindamycin.

Follow-up and outcomes

The mean follow-up was 69 months (interquartile range 48–72 months). Ten (66.7%) patients achieved complete healing of the