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Original

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Dalbavancin for treating prosthetic joint infections caused by Gram-positive bacteria: A proposal for a low dose strategy. A retrospective cohort study

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ABSTRACT

Background. Gram-positive bacteria are the leading cause of prosthetic joint infection (PJI). Dalbavancin is a lipoglycopeptide with remarkable pharmacokinetic properties and high bactericidal activity against most Gram-positive bacteria. Although clear evidence regarding its effectiveness in bone and joint infections lacks, recent studies suggest a promising role of dalbavancin in PJI.

Methods. From June 1st 2016 to May 1st 2018, all patients diagnosed of PJI and treated with DAL alone or in combination with other drugs were retrospectively evaluated. Dalbavancin susceptibility of every isolate was studied following CLSI criteria. The primary objective was to assess the clinical efficacy and tolerability of the drug in patients with PJI. A cost-analysis was performed following the DALBUSE study methodology.

Results. Sixteen patients were treated with dalbavancin, eight with total hip arthroplasty infection (THAi) and eight with total knee arthroplasty infection (TKAi). *Staphylococcus* spp. and *Enterococcus* spp. were the microorganisms involved. No major side effects were detected. Infection resolved in 12 patients. In 2 patients the treatment failed, and another patient died due to unrelated causes. One patient is currently being treated for hematogenous-spread knee infection secondary to prosthetic aortic arch endocarditis. After discontinuation of dalbavancin, and excluding patients who died or with clinical failure, the median follow up of the cohort was 503 days (interquartile range IQR, 434.5 to 567 days). We calculate that US$ 264,769 were saved.

Conclusion. This study suggests that dalbavancin treatment for PJI caused by Gram-positive bacteria is a safe and effective option that reduces hospital stay and costs. Future reports are needed to confirm these findings.

Keywords: Prosthetic joint infection, dalbavancin, safety, efficacy

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Dalbavancina para el tratamiento de infección periprotésica causada por microorganismos grampositivos. Propuesta para una estrategia con dosis bajas. Un estudio retrospectivo de cohortes

RESUMEN

Introducción. Las bacterias grampositivas son la principal causa de infección periprotésica (IPP). Dalbavancina es un lipoglicopéptido con interesantes propiedades farmacocinéticas y una importante actividad bactericida frente a la mayoría de gram positivos. Aunque aún necesitamos mayor evidencia en relación con su uso en infección osteoarticular, estudios recientes sugieren un papel importante de dalbavancina en la IPP.

Métodos. Desde el 1 de Junio de 2016 al 1 de Mayo de 2018, todos los pacientes diagnosticados con IPP y tratados con dalbavancina sola o en combinación con otros fármacos fueron evaluados de forma retrospectiva. La sensibilidad a dalbavancina de los aislamientos fue evaluada según las recomendaciones de CLSI. El objetivo primario fue determinar la eficacia y tolerabilidad del fármaco en pacientes con IPP. Se realizó un análisis de coste siguiendo la metodología descrita en el estudio DALBUSE.

Resultados. Dieciséis pacientes fueron tratados con dalbavancina, ocho con infección de prótesis total de cadera y ocho con infección de prótesis total de rodilla. *Staphylococcus* spp. y *Enterococcus* spp. fueron los microorganismos implicados. No hubo efectos adversos relevantes. La infección se resolvió en 12 pacientes. En dos pacientes el tratamiento falló, y otro paciente falleció por causas no relacionadas. Un

paciente es actualmente en tratamiento supresor por infección por diseminación hematógena de prótesis total de rodilla a partir de endocarditis protésica aórtica. Tras la discontinuación de dalbavancina, y exceptuando los pacientes fallecidos y/o con fallo terapéutico, el seguimiento medio fue de 503 dias (rango intercuartílico 434.5-567 dias). Se estimó un ahorro de 264.769 dólares USA.

Conclusiones. Este estudio sugiere que dalbavancina para el tratamiento de IPP causada por microorganismos gram positivos es segura y una opción eficaz que reduce la estancia hospitalaria y los costes. Se precisan más comunicaciones para confirmar estos datos.

Palabras clave: infección periprotésica, dalbavancina, seguridad, eficacia

INTRODUCTION

Total joint arthroplasty is a widely used treatment modality for knee (TKA) and hip (THA) osteoarthritis. In 2010, more than 310,800 THA and 639,400 TKA were performed in the United States. Prosthetic joint infection (PJI) is a major complication, ocurring in 1-2% of primary joint arthroplasties and up to 10% of revision surgeries [1, 2].

Dalbavancin (DAL) is a lypoglycopeptide structurally related to teicoplanin, approved for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) with bactericidal activity against most Gram-positive microorganisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) [3]. Recent studies show that DAL is an effective option to be considered in patients with bacteriemia, endocarditis and osteoarticular infections [4].

Given the few reports on DAL administration for PJI, its dosage scheme is not standardized. However, its unique capacity to achieve high and stable concentrations in bone and peri-articular tissues [5] allows prolonged and cost-effective [6] treatment of PJI caused by Gram-positive microorganisms.

MATERIAL AND METHODS

From June 1st 2016 to May 1st 2018, all patients older than 18 years of age, diagnosed of PJI in our institution and treated with DAL were retrospectively reviewed. The primary objective was to assess the clinical efficacy and tolerability of the drug when used in real life to treat PJI. PJI cases were diagnosed following the International Consensus Meeting on Prosthetic Joint Infections diagnostic criteria [7]. At least one year of follow-up without clinical relapse was required after DAL was withdrawn to consider PJI to be cured.

Currently, PJI is an off-label indication of DAL. Patients were appropriately informed about using DAL as an off-label medication for PJI, its potential toxicity and the reasons for choosing DAL in each particular case, generally, because of failure of other antibiotics, their toxicity, interactions and/or unavailability of other orally-administered choices. Informed consent was obtained from all patients included in the study. The study protocol was approved by the Institutional Ethics Committee (research approval reference number: 2018)

Staphylococcus spp. susceptibility to DAL and *E. faecalis* susceptibility to vancomycin were confirmed by the E-test method, following CLSI criteria. However, antimicrobial concentrations that confirm susceptibility of *Enterococcus faecium* to DAL and *Enterococcus faecalis* to vancomycin are not well defined according to CLSI and EUCAST guidelines [8].

RESULTS

Table 1 shows the main clinical features of the cohort. A total of 16 patients (9 males, 56%) were included in the analysis. Median age was 76 years and median age-adjusted Charlson index was 3 (IQR 3-5) (see table 2). Coagulase-negative staphylococci (CoNS) were the most commonly isolated microorganisms (7 cases, 43.7%), followed by MRSA and *E. faecium* with four cases (25%), while *E. faecalis* was involved in only one case (6.25%). THAi and TKAi occurred in 8 patients each. Eleven cases (68.7%) were considered chronic PJI. Seven patients (43.7%) were treated with two-stage revision arthroplasty and antibiotic-impregnated articular spacers. Two patients needed surgical debridement (patients #5 and #10, table 1) due to comorbidities; Patient five had undergone a resection arthroplasty months before and drainage of the abscess and diaphysitis was performed with no prosthesis reimplantation due to poor bone stock. Two patients (patients # 7 and #16) were treated with suppressive antimicrobial treatment, but no surgery.

The reasons for choosing DAL in each patient are detailed in table 1. DAL was used as monotherapy in 11 patients (68.7%). One patient received DAL in association with oral rifampicin that was ultimately discontinued because of hepatic toxicity. Four patients received oral dicalcic fosfomycin in an outpatient basis concurrent with DAL, without showing major side effects. In most cases, rifampicin could not be used, mainly because of interactions with oral anticoagulants (3 out of 11) and immunosuppressive drugs for solid organ transplantation (patient number 13, table 1, one out of eleven).

A total of 9 patients (56%) received 1.5 g of DAL as loading dose, followed by 0.5 g at day seven, and then 0.5 g every two weeks for two months in THAi and for three months in TKAi. This treatment scheme was termed *Low Dose Bi-weekly Dalbavancin*, or *LDBD*. Once DAL therapy ended, and after excluding patients who died or had clinical failure (table 1) were followed for a median 503 days (interquartile range IQR, 434.5 to 567 days). Side effects attributable to medication were on one case of mild skin macular rash and one case of mild transient leukopenia.

Excluding one patient, who died of an unrelated cause at three months of follow up (patient #10, table 1), currently, 12 patients (80%) show no clinical, pathological, biochemical, microbiological and/or gammagraphic signs of infection. Two different strains of previously identified microorganisms were found in different tissue samples obtained from two patients

Table 1 Clinical characteristics of the patients treated with dalbavancin

Patient #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Age	66	80	75	69	77	87	77	69	70	92	78	85	71	83	71	75
Sex	M	M	M	M	F	M	F	F	M	M	F	F	F	M	F	M
Charlson	2	5	2	3	3	7	3	3	3	5	3	7	5	7	3	4
Infection	Early THAi	Ch TKAi	Ch THAi	UIPC (THA)	Dyaphisitis after G	Ch THAi	UIPC (TKA)	Ch THAi	Ch THAi septic pseudoarthrosis	Ch TKAi	Ch THAi	Ch TKAi	Acute hem TKAi	Acute hem TKAi	Early TKAi	Acute hem TKAi (IE)
Surgery	2SE AIAS	2SE AIAS	G	2SE AIAS	Drainage	G	NONE (supressive treatment)	2SE AIAS	2SE AIAS	Drainage	2SE AIAS	Prosthesis removal & Arthrodesis	DAIR	Prosthesis removal AIAS	2SE AIAS	NONE (supressive tratment)
Aetiology	MSSA & CoNS	MSSA & MRSA	Ef	Ef	MSSA	Ef	CoNS	Se	Ef and Se	MRSA	Se	MRSA & Se	Se	Ef	MRSA	Efa
Reasons for DAL use	NOBCA	INT& TOX	FOC	TOX	FOC	NOBCA	NOBCA	NOBCA	FOC	NOBCA	NOBCA	NOBCA	NOBCA &INT	NOBCA &INT	NOBCA &INT	NOBCA
DAL dosing	1g day 1 0.5g 10w	1g day1 1g 8w	1g day 1 1g 12w	1g day 1 0.5g 8w	1g day 1 0.5 g 6w	1g day 1 0.5 g 6w	LDBD	LDBD	LDBD	LDBD	LDBD	LDBD	LDBD	LDBD	LDBD	-1.5 g day 1 and day 7 -1.5 g biweekly four months -Then 1.5 g monthly
Side effects	-	-	-	-	-	-	Leukopenia	-	-	-	-	Rash	-	-	-	-
Days of follow up since DAL stop	498	777	647	592	540	542	422	447	467	94	Clinical faliure	508	70	350	313	Ongoing
Outcome	C	C	C	C	C	C	Ongoing (Read text)	C	C	Died (unrelated)	Fa	C	F	C	C	Ongoing (read text)

[a]CoNS obtained from surgical samples showed clinical susceptibility after clinical failure. Ef: *Enterococcus faecium*, Efa: *Enterococcus faecalis*. IE: infective endocarditis, 2SE: 2 stage Exchange, AIAS: antibiotic impregnated articulated spacer, C: Cured, Ch: Chronic, CF: Clinical failure, CoNS: coagulase-negative staphylococci, INT: Interactions, FOC: Failure with other choices, G: Girdlestone, LDBD: Low dose biweekly DAL: 1.5 g. day1, 0.5 g. day7, then biweekly, NOBCA: No oral better choice available, Se: *Staphylococcus epidermidis*, THAi: Total hip arthroplasty infection, TKAi: Total knee arthroplasty infection, TOX: Toxicities, UIPC: unsuspected intraoperative positive cultures, W: weeks

Table 2 **Baseline patient characteristics (n=16)**

Characteristic	n (%)[a]
Age (years) [median (IQR)]	76 (70.25-82.25)
Male sex; n (%)	9 (56.2)
Underlying diseases; n (%)	
Diabetes mellitus	2 (12.5)
Cardiovascular disease	4 (25)
Respiratory tract disease	1 (6.2)
Neurological disorder	4 (25)
Immunosuppressive therapy	2 (12.5)
Solid organ transplantation	1 (6.2)
Haematological malignancy	1 (6.2)
Chronic renal failure	3 (18.7)
Psiquiatric disorders	2 (12.5)
Oral anticoagulation	4 (25)
Age-adjusted Charlson CI [median (IQR)]	3 (3-5)
Surgical approach; n (%)	
No surgery	2 (12.5)
DAIR	2 (13.3)
One stage	0 (0)
Two stage	8 (53.3)
Girdlestone	2 (13.3)

[a]Data are n (%) unless otherwise stated; IQR, interquartile range; HIV, human immunodeficiency virus.

at the moment of revision surgery. Neither of them presented with clinical symptoms suggestive of persistence of infection nor polymorphonuclear infiltration in the pathological examination. None of them showed non-susceptibility to DAL according to the CLSI criteria.

We calculate that a total of 571 days of hospitalization were avoided by using DAL, as an alternative to daptomycin, which requires prolonged hospitalization for daily intravenous administration. By applying the criteria used in the cost analysis reported by Bouza et al (the DALBUSE study [8]), we estimate a total cost reduction of US$ 264,769.

DISCUSSION

Surgery along with antimicrobial therapy is the cornerstone for the treatment of PJI. Removal of the prosthesis, either as primary treatment or at revision surgery, is almost always necessary in order to achieve a definitive cure of the infection. Since Gram-positive microorganisms are most commonly involved in PJI (especially *Staphylococcus* and *Enterocuccus* spp) [9] appropriate antibiotics need to be chosen [10].

According to previous reports [9], DAL exhibits high effectiveness against Gram-positive microorganisms causing PJI. The use of DAL in such cases allows earlier hospital discharge, thus reducing the length of stay and cost.

Biedenbach et al analyzed the activity of DAL against a large collection of Gram-positive microorganisms: The minimal inhibitory concentration$_{90}$ (MIC_{90}) for *S. aureus* was 0.06 mg/L, and 99.9% of microorganisms were inhibited at concentrations of 0.12 mg/L. The MIC_{90} was 0.06 mg/L and 0.12 mg/L for oxacillin-susceptible and oxacillin-resistant CoNS, respectively. For *E. faecalis* and *E. faecium*, the MIC_{90} values were, 0.06 and 0.12 mg/L, respectively. Thus, bactericidal concentrations in plasma, bone and peri-articular tissues are achievable with usual therapeutic concentrations [11]. Special attention deserves the fact that the activity of DAL against CoNS isolates with teicoplanin MIC values higher than 8 mg/L may be impaired, and teicoplanin MIC values higher than 16 mg/L almost invariably results in DAL non-susceptibility[12].

Another important issue is DAL activity against bacterial biofilms in PJI. DAL has proved in *in vitro* models to be a powerful inhibitor of bacterial colonies, in which structural and functional bacterial differentiation, once embedded in the extracellular matrix, promote microorganisms to be highly resistant to antibiotics whether or nor they were primarily susceptible to the drug [13].

Another relevant aspect of the antibiotic treatment in PJI is the ability of the drug to reach adequate and stable concentrations in bone and peri-articular tissues. A phase I trial evaluated the penetration of DAL in bone and articular tissues in healthy patients who received DAL up to 14 days before elective orthopedic surgery. Bone concentration of DAL measured 12 hours and 14 days post-dose were 6.3 µg/dl and 4.1 µg/dl, respectively, much higher than MIC_{90} of target microorganisms in PJI [5]. A two-dose 1.5 g once a week regimen was proposed for the treatment of acute osteomyelitis, in a single-center open-label study comparing DAL with standard treatment. *Staphylococcus* spp. and *Enterococcus* spp. were the causative agents of 91% of cases. The outcomes reported suggest that DAL was highly effective and safe for treating acute osteomyelitis. However, patients with prosthetic implants at the site of infection were excluded in this study [14].

Recently, a Spanish multicenter real life experience with the use of DAL in different clinical settings has been published. It included 20 cases of PJI retrospectively collected in one year from 29 national institutions that presented favorable clinical outcomes [9]. Again, *Staphylococcus* spp. and *Enterococcus* spp. were the etiological agents of 90% of the PJI cases. Eighty percent of the cases exhibited a "successful clinical outcome". However, no specific data regarding DAL dosing scheme was provided.

In our institution, DAL was firstly used for the treatment of PJI in June 2016. Most of the clinical experience previously cited was not available at that moment, and there were no standard recommendations for dosage. Throughout the following two years, 15 cases of PJI were treated with DAL. As mentioned, most of them were elderly patients with complex co-morbidities. The first six cases were treated with DAL 1.5g every week, for a variable period of time. As we gained experience, we turned to a regimen of 1.5g at day 1 and 0.5g at day 7, followed by 500 mg every two weeks for two months in THA infections and for three months in TKA infections (LDBD). This treatment scheme is supported by the fact that DAL concentration in bone and peri-articular tissues after 14 days of administration are high enough for Gram-positive microorganism inhibition [5], and patients markedly improve following the first two doses. Whether just two doses of DAL are enough for infection control remains a controversial issue. According to the study by Rappo et al, patients with PJI who underwent surgical removal of the prosthesis and debridement, in one or two stages, fared well after two doses of DAL in acute osteomyelitis. On the basis of this published experience and supported by the favorable outcome of our first cases, we decided to use the LDBD as the standard regimen in our institution.

One of the reasons for choosing DAL was the unavailability of other orally administered antibiotics for this indication (table 1). Ideally, rifampicin should be added to any therapeutic regimen for PJI after surgeries with prosthesis retention, due to its activity against Gram-positive bacterial biofilms [10]. In our case series, reasons for not using rifampicin were resistance and/or interactions that precluded its use: three patients were taking oral anticoagulants, and another three were taking drugs with major interactions, including a patient who was a kidney trasplant recipient receiving immunosupressive drugs. DAL remained effective even though rifampicin could not be used. Oral (dicalcic) fosfomycin was used in three cases caused by MRSA, *E. faecalis* and CoNS, presenting no major side effects. We did not use trimethoprim-sulfamethoxazole because CoNS are commonly resistant, and the presence of gross purulence favors its failure [15]. There were reasons for choosing DAL instead of linezolid: half of the patients were taking serotonin reuptake inhibitors, with the consequent risk of serotoninergic syndrome [16], and five patients showed preexisting anemia and/or chronic kidney disease [17], and another patient had a myelodysplastic syndrome.

Four of our cases deserve a special comment. In the first case (case #13), a 71 year-old woman, who had received a kidney transplant three months before, developed an acute hematogenous prosthetic knee infection originating from a subclavian venous catheter infection, that had been used for hemodyalisis until transplantation surgery, which had remained placed for the treatment of mild rejection, caused by an oxacillyn-resistant CoNS that could be isolated from blood, periprosthetic effusion and the subclavian catheter tip. Debridement and retention with mobile elements exchange was performed. Three months after DAL administration had been discontinued, C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values were normal. However, six months afterwards, recurrent infection was suspected due to inflammatory signs and the presence of peri-prosthetic abscess. A two-stage revision arthroplasty was performed. All samples yielded *Staphylococcus* species, different from the one previously isolated, but fully susceptible to DAL.Interestingly, this patient did not receive rifampicin due to major interactions with immunosupressive drugs. In the other three patients the prosthesis was not removed for different reasons, a clinical scenario in which treatment failure is likely. In case #7, a 77 year-old woman developed an acute TKA infection. The patient refused revision surgery and DAL monotherapy was then used: 1,500 mg were administered at day 1 and 7, then every two weeks for 6 months. After 373 days of follow up, there are no signs of clinical relapse, and ESR and CRP values are normal with knee function preserved. In case #10, a 95 year-old man with a chronic TKA PJI and surrounding soft tissues infection caused by MRSA was treated with DAL monotherapy with LDBD. Surgery was not performed because of advanced dementia. Clinical response was remarkable, with functional improvement of the affected knee and normalization of CRP after the first two doses of LDBD. After the third and fourth doses, he was changed to oral cotrimoxazole. He died two months later due to unrelated causes with no clinical signs of relapse. In case #16, a 75 year-old man was diagnosed of prosthetic aortic arch infective endocarditis (Bono-Bentall procedure) with secondary haematogenous TKA infection caused by *E. faecalis* (positive in blood cultures and sinovial fluid) with a confirmatory PET-CT scan. Cardiac surgery was discarded due to excessive surgical risk. After receiving intravenous ampicillin and ceftriaxone, followed by daptomycin and fosfomycin (because of

ampicillin-associated reversible leukopenia), he was ultimately changed to 1.5 g of DAL on day 1 and 7, then 1.5 g every two weeks and then suppressive treatment with a monthly dose of 1.5 g. After the fifth monthly dose, hematocrit, CRP and ESR have returned to normal values and the patient has no symptoms or signs of clinical relapse.

DAL is effective against *Staphylococcus* spp, and clear susceptibility breakpoints are well established in both CLSI and EUCAST recommendations [7, 10]. Clinical reports and in vitro experiments show that DAL is highly bactericidal against susceptible enterococci [18] and has activity against biofilms formed by DAL-susceptible enterococci [19-20]. However, no susceptibility breakpoints have been determined yet by CLSI or EUCAST for vancomycin-resistant *E. faecalis* and *E. faecium*. Nevertheless, based on previous clinical reports and lacking potentially better and safer options, DAL was successfully used in five cases. Our experience is in line with previous reports regarding DAL efficacy for the treatment of enterococcal infections.

As previously reported, toxicity attributable to DAL administration was negligible. No major side effects were detected, apart from mild transient grade I leukopenia and a mild transient rash in one patient. DAL therapy allowed early discharge of most of the patients, with a presumably relevant impact in terms of healthcare costs. Applying the same cost analysis previously reported by Bouza et al. in the DALBUSE study, we calculated that 571 days of hospitalization were avoided, and a total of US$ 264,769 were saved.

Our study has important limitations. It reflects a single center experience and potential biases may be present. Nevertheless, the data presented reflect real life experience with DAL in treating PJI with a homogeneous dosing scheme. Safety, tolerability and efficacy were excellent. In the absence of a clinical trial, this case series presents the results of a cohort patients with complex co-morbidities and difficult to treat microorganisms. In our view, DAL therapy allowed clinicians to deal with PJI cases in which no other options aside from daptomycin and vancomycin were available, providing patients with a safe, comfortable and effective outpatient treatment resulting in excellent outcome.

To our knowledge, this is the largest single center report on the use of DAL for PJI. Currently, no standard recommendation regarding dosage and duration of treatment exists. Our experience shows that DAL administration for treating Gram-positive PJI allows earlier discharge, reducing hospital stay, and seems to be safe, effective and cost saving. Besides, our study suggests that DAL administration every two weeks (the LDBD regimen) seems to be an effective dosing scheme. Our preliminary results and the true role of DAL in the treatment of PJI should ideally be confirmed by future studies.

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CONFLICT OF INTEREST

LBM has received lecture fees from Angelini Pharmaceuticals. No other conflict of interest is reported.

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