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Dalbavancin treatment for prosthetic joint infections in real-life: a national cohort study and literature review

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ABSTRACT

Objectives: Dalbavancin is a long-lasting lipoglycopeptide active against Gram-positive bacteria, especially methicillin-resistant staphylococci. Few data are available on dalbavancin use for treatment of prosthetic joint infections (PJIs). We describe a cohort of patients treated for PJI with dalbavancin and review the literature regarding this condition.

Methods: All adult patients with PJI from the French dalbavancin national cohort from 1 June 2017 to 1 January 2019 were included. We collected clinical and microbiological characteristics and outcome through a standardised questionnaire. Clinical cure was defined as absence of clinical signs of infection at last visit. Failure was a composite criterion defined by persistence or reappearance of signs of infection, and/or switch to suppressive antibiotic treatment and/or death from infection. The literature review was performed using PubMed.

Results: Seventeen patients were included. Bacteria were identified in 16 cases: *Staphylococcus aureus* ($n = 10$), including methicillin-resistant *S. aureus* ($n = 1$); and coagulase-negative staphylococci ($n = 10$), including methicillin-resistant *Staphylococcus epidermidis* ($n = 4$). Sixteen patients (94.1%) had received antibiotic therapy prior to dalbavancin use (mean of 2.2 ± 1.3 lines). Clinical cure was achieved in 8/17 patients after a median follow-up of 299.0 (IQR 97.0–476.0) days. We reviewed all cases of PJI treated with dalbavancin available in the literature and the overall clinical cure was estimated at 73.1%.

Conclusion: Our study and literature data suggest that use of dalbavancin in PJI could be considered, even as salvage therapy. Dalbavancin appears to be a safe and easy treatment for patients with staphylococcal PJIs.

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1. Introduction

Dalbavancin is a lipoglycopeptide antibiotic with broad-spectrum activity against Gram-positive bacteria, especially methicillin-resistant *Staphylococcus aureus* [1,2], and long-lasting activity (15 days). The pharmacokinetic properties and administration patterns of dalbavancin could be useful for the treatment of bone and joint infections, especially prosthetic joints infections (PJIs) [3]. Moreover, some in vitro models have shown that dalbavancin is active against staphylococci in biofilms [4]. To date, only a few clinical data are available for PJIs [5,6].

Here we describe a series of patients treated for a PJI with dalbavancin among a previously described national cohort [7].

2. Materials and methods

Patients treated with dalbavancin for PJI were selected from the study population previously included in the 'French national cohort of first use of dalbavancin' [7]. All adult patients with PJI treated with at least one dose of dalbavancin from 1 June 2017 to 1 January 2019 were included. The prescribers noted in a standardised questionnaire the following information: type of PJI; specimen results and microbiological characteristics; reason(s) for dalbavancin use; dose and duration of dalbavancin treatment; adverse drug reactions; and outcome at last visit.

Patients were informed that their clinical data could be used, after anonymisation, for research purposes. The research was conducted in accordance with the Declaration of Helsinki.

Immunosuppression was defined as the presence of asplenia, neutropenia, agammaglobulinemia, organ transplant, haematological malignancy, known human immunodeficiency virus (HIV) infection and CD4⁺ count <400/mm³, or Child–Pugh class C cirrhosis. We considered corticosteroid use (i.e. daily dose >20 mg of prednisolone or equivalent), chemotherapy, cyclophosphamide, azathioprine and cyclosporine as immunosuppressive treatments. Liver failure was defined by coagulation factor V level ≤50% and/or hepatic encephalopathy.

Dalbavancin minimum inhibitory concentrations (MICs) were determined by the agar dilution or broth microdilution method. Breakpoints were as defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [8].

Outcome was evaluated by the investigators at the patient's latest visit. Clinical cure was defined as the absence of clinical signs of infection confirmed by the physician in charge. Failure was a composite criterion defined as persistence or reappearance of signs of infection (with or without microbiological identification), and/or switch to suppressive antibiotic treatment and/or death from infection.

A literature review was performed in the PubMed database using the search terms 'dalbavancin', 'bone and joint infection', 'prosthetic joint infection' and 'implant-associated infections'. We considered cure status as stated by the study authors, and all others status as failures. When no data were specific to the PJI population, they were considered as unavailable. Patients with implant-associated infections were included in the literature review, except for overall outcome [5].

Quantitative variables are presented as the mean ± standard deviation or the median and interquartile range (IQR). Qualitative variables are presented as the number of occurrences and relative frequencies. All statistical analyses were performed using SPSS Statistics v.17.0 (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 17 patients from eight French hospitals were included in the study. Table 1 presents the patients' characteris-

tics at baseline and reasons for dalbavancin use according to outcome.

The main types of PJI were hip prosthesis ($n = 8$; 47.1%) and knee prosthesis ($n = 6$; 35.3%). Bacteria were documented in 16/17 cases, including 5 polymicrobial infections, with Gram-negative bacteria in 3 cases. *Staphylococcus aureus* was isolated in 10 cases (62.5%), with methicillin resistance in only 1 case (6.3%), and coagulase-negative staphylococci (CoNS) also in 10 cases (62.5%), with methicillin resistance in 4 cases (25.0%). Four patients (23.5%) presented concomitant bacteraemia.

The median MICs of dalbavancin were 0.064 mg/L (range, 0.047–0.064 mg/L) for *S. aureus* and 0.023 mg/L (range, 0.006–0.094 mg/L) for CoNS, without difference according to susceptibility to methicillin.

Among the 17 patients, 16 received surgical management associated with antibiotic therapy, which was mostly (9/16) debridement and implant retention (DAIR). The median number of previous surgeries for septic reason on the site before dalbavancin use was 1.5 in the cure group and 3.0 in the failure group.

Only one patient received dalbavancin as first-line treatment. The median duration of previous antibiotic therapy was 34.5 days (IQR, 31.3–46.8 days).

The most frequent reason for dalbavancin use was an adverse event of previous antibiotic treatment ($n = 8$). Dalbavancin was also used to simplify the treatment to allow an early hospital discharge ($n = 5$), to better adherence ($n = 4$), to improve patient's autonomy ($n = 3$) or because of impossible venous access ($n = 2$). Finally, two patients had bacteria resistant to the previous antibiotic treatment, and only one patient had clinical failure of previous antibiotic treatment.

The preferential administration scheme of dalbavancin was 1500 mg at Day 1 and 1500 mg at Day 7 ($n = 8$; 47.1%). The different dalbavancin treatment regimens are described in Table 1.

Dalbavancin was prescribed as monotherapy in eight patients (47.1%). In the 9 remaining patients, associated antibiotics used were tetracyclines ($n = 3$; 33.3%), trimethoprim/sulfamethoxazole ($n = 2$; 22.2%), fluoroquinolones ($n = 2$; 22.2%), rifampicin ($n = 1$; 11.1%) and clindamycin ($n = 1$; 11.1%). No adverse events among the 17 patients were reported.

The median (IQR) duration of follow-up was 299.0 (97.0–476.0) days. Latest patient evaluation showed clinical cure in 8/17 patients, among whom 6 received dalbavancin as monotherapy. Two patients died due to PJI. Four relapses were reported, including three without microbiological identification and one superinfection. Lastly, three patients received an antibiotic suppressive treatment, including two patients who received dalbavancin as outpatient parenteral antimicrobial therapy (OPAT) at hospital discharge.

The main difference between the cure and failure groups was the number of severe patients in the failure group, with one sepsis, one septic shock and one patient managed without surgery.

Table 2 presents all cases of PJI treated with dalbavancin available in the literature. Most studies reported patients with various infectious diseases due to Gram-positive cocci, including skin and soft-tissue infections and bone and joint infections. A total of 102 Gram-positive cocci-related PJIs were reported, with a predominance of CoNS ($n = 59$). Regarding the scheme of dalbavancin administration, 1000 mg followed by 500 mg weekly was used in most cases. The overall clinical cure was estimated at 73.1% ($n = 68/93$, excluding the results of the study by Morata et al. as the specific rate of clinical cure in PJIs was not described in their article).

4. Discussion

Optimal management of PJIs is the combination of surgery and effective antibiotic therapy based on microbiological documenta-

Table 1
Demographics, baseline characteristics and description of dalbavancin use in study patients

Characteristic	Total (N = 17)	Success (N = 8)	Failure (N = 9)
Age (years) [median (IQR)]	69.0 (62.0–75.0)	66.5 (60.5–71.3)	73.0 (64.0–80.0)
Sex ratio (M/F)	1.43	3.00	0.80
Length of hospitalisation (days) [median (IQR)]	15.5 (9.3–25.0)	17.0 (8.5–27.5)	14.0 (10.5–19.5)
Co-morbidities [n (%)]			
Heart failure	5 (29.4)	4 (50.0)	1 (11.1)
Chronic renal failure	4 (23.5)	3 (37.5)	1 (11.1)
Liver failure	2 (11.8)	1 (12.5)	1 (11.1)
Neurological disease	2 (11.8)	2 (25.0)	0 (0)
Immunosuppression	6 (35.3)	3 (37.5)	3 (33.3)
Cancer chemotherapy	1 (5.9)	1 (12.5)	0 (0)
Immunosuppressive treatment	1 (5.9) ^a	0 (0)	1 (11.1)
Diabetes mellitus	4 (23.5)	2 (25.0)	2 (22.2)
Renal clearance (mL/min) [median (IQR)]	87.5 (56.9–104.4)	88.3 (52.5–101.4)	87.5 (58.8–104.4)
Site of prosthesis [n (%)]			
Hip	8 (47.1)	4 (50.0)	4 (44.4)
Knee	6 (35.3)	4 (50.0)	2 (22.2)
Shoulder	1 (5.9)	0 (0)	1 (11.1)
Ankle	1 (5.9)	0 (0)	1 (11.1)
Elbow	1 (5.9)	0 (0)	1 (11.1)
Positive blood cultures [n (%)]	4 (23.5)	1 (12.5)	3 (33.3)
Severity [n (%)]			
Septic shock	1 (5.9)	0 (0)	1 (11.1)
Volume expansion	1 (5.9)	0 (0)	1 (11.1)
Before dalbavancin treatment			
Biological analysis [median (IQR)]			
White blood cell count (× 1000/L)	8.5 (7.1–10.9)	8.4 (7.0–10.3)	8.5 (8.1–14.3)
Haemoglobin (g/dL)	10.6 (9.6–12.9)	10.3 (9.4–11.6)	11.8 (9.8–13.3)
Absolute neutrophil count (× 1000/L)	5.8 (5.0–8.2)	5.5 (5.3–6.9)	6.0 (4.7–10.3)
Eosinophil count (× 1000/L)	0.2 (0.1–0.4)	0.3 (0.2–0.4)	0.2 (0.1–0.2)
C-reactive protein (mg/L)	41.0 (18.3–75.8)	21.0 (13.0–58.0)	41.0 (30.5–123.0)
Surgical treatment [n (%)]			
DAIR	9 (52.9)	5 (62.5)	4 (44.4)
Exchange	5 (29.4)	2 (25.0)	3 (33.3)
Synovectomy	1 (5.9)	1 (12.5)	0 (0)
Joint aspiration	1 (5.9)	0 (0)	1 (11.1)
Previous antibiotic treatments [n (%)]	16 (94.1)	8 (100)	8 (88.9)
Number of lines [median (IQR)]	2.0 (1.0–3.0)	3.0 (1.8–4.0)	2.0 (1.0–3.0)
Duration (days) [median (IQR)]	34.5 (31.3–46.8)	33.0 (31.5–41.5)	36.0 (28.5–46.5)
Microbiology analysis [n (%)]			
Documented infections	16 (94.1)	7 (87.5)	9 (100)
Polymicrobial infections	5 (31.3)	2 (28.6)	3 (33.3)
<i>Staphylococcus</i> spp.	16 (100)	7 (100)	9 (100)
<i>Staphylococcus aureus</i>	10 (62.5)	5 (71.4)	5 (55.6)
Methicillin-resistant <i>S. aureus</i>	1 (6.3)	1 (14.3)	0 (0)
Coagulase-negative staphylococci	10 (62.5)	4 (57.1)	6 (66.7)
<i>Staphylococcus epidermidis</i>	7 (43.8)	3 (42.9)	4 (44.4)
Methicillin-resistant <i>S. epidermidis</i>	4 (25.0)	2 (28.6)	2 (22.2)
<i>Enterococcus faecalis</i>	1 (6.3)	1 (14.3)	0 (0)
Reason for dalbavancin use [n (%)] ^b			
Clinical failure of previous antibiotic treatment	1 (5.9)	1 (12.5)	0 (0)
Adverse event of previous antibiotic treatment	8 (47.1)	4 (50.0)	4 (44.4)
Bacteria resistant to previous antibiotic treatment	2 (11.8)	0 (0)	2 (22.2)
Impossible venous access	2 (11.8)	1 (12.5)	1 (11.1)
Patient's autonomy	3 (17.6)	1 (12.5)	2 (22.2)
Early hospital discharge	5 (29.4)	1 (12.5)	4 (44.4)
Better compliance	4 (23.5)	1 (12.5)	3 (33.3)
Dalbavancin dosing regimen [n (%)]			
1 dose, 1.5 g	3 (17.6)	2 (25.0)	1 (11.1)
2 doses, 7-day interval, 1.5 g × 2	8 (47.1)	4 (50.0)	4 (44.4)
2 doses, 14-day interval, 1.5 g, 1 g	1 (5.9)	0 (0)	1 (11.1)
3 doses, 7-day interval, 1.5 g × 3	1 (5.9)	0 (0)	1 (11.1)
7 doses, 7-day interval, 1 g × 1, 0.5 g × 6	1 (5.9)	1 (12.5)	0 (0)
10 doses, 14-day interval, 1 g × 1, 0.5 g × N	1 (5.9)	1 (12.5)	0 (0)
Suppressive, 21-day interval	2 (11.8)	0 (0)	2 (22.2)
1.5 g × 1, 0.5 g × N	1 (5.9)	0 (0)	1 (11.1)
1.5 g × 3, 0.5 g × N	1 (5.9)	0 (0)	1 (11.1)

IQR, interquartile range; DAIR, debridement, antibiotics and implant retention; N: number of subsequent doses.

^a Methotrexate followed by corticosteroid treatment.

^b Patients could have several reasons for dalbavancin use.

Table 2
Review of studies of prosthetic joint infections (PJIs) treated by dalbavancin: bacteria, preferential administration regimen and outcome

Author, year	Method	PJI [n (%)]	Bacteria involved [n (%)]	Preferential scheme [n (%)]	Monotherapy [n (%)]	Cure [n (%)]
Bouza et al., 2018 [11]	Multicentric retrospective study All infections treated with dalbavancin (Spain)	n = 20/69 (29.0%)	MRSA (n = 3; 15.0%) MSSA (n = 1; 5.0%) CoNS (n = 13; 65.0%) <i>Enterococcus</i> sp. (n = 1; 5.0%) Other (n = 1; 5.0%) Negative culture (n = 1; 5.0%)	N/A	N/A	16/20 (80.0%)
Wunsch et al., 2019 [10]	Multicentric retrospective study All infections treated with dalbavancin (Austria)	n = 32/101 (31.7%)	N/A	N/A	N/A	29/32 (90.6%)
Morata et al., 2019 [5]	Multicentric retrospective study All BJIs treated with at least one dose of dalbavancin (Spain)	PJI, n = 19 Implant-associated infection, n = 45	Among the implant-associated infection group (n = 45): Polymicrobial (n = 5; 11.1%) <i>Staphylococcus epidermidis</i> (n = 26; 57.8%) MSSA (n = 4; 8.9%) <i>Staphylococcus lugdunensis</i> (n = 2; 4.4%) <i>Staphylococcus capitis</i> (n = 1; 2.2%) <i>Streptococcus pneumoniae</i> (n = 1; 2.2%) <i>Enterococcus faecalis</i> (n = 4; 8.9%) <i>Enterococcus faecium</i> (n = 3; 6.4%) <i>Corynebacterium striatum</i> (n = 2; 4.4%) Anaerobes (n = 2; 4.4%) Negative culture (n = 3; 6.7%)	N/A	Implant-associated infection group, (15/45; 33.3%)	Among the implant-associated infection group (n = 45): 31/45 (68.9%) - Implant retention (n = 15; 33.3%) - Implant removal (n = 16, 35.6%)
Tobudic et al., 2019 [9]	Monocentric retrospective study SSTI and BJI treated with dalbavancin (Austria)	n = 8/72 (11.1%)	N/A	1500 mg d1, followed by 1000 mg every 14 days (n = 7; 87.5%) 1000 mg d1, followed by 500 mg weekly (n = 1; 12.5%) Duration median (range): 12 (6–32) weeks	N/A	3/8 (37.5%)
Buzón Martín et al., 2019 [6]	Monocentric retrospective study PJI treated with dalbavancin (Spain)	n = 16	CoNS (n = 7; 43.8%) MRSA (n = 4; 25.0%) <i>E. faecium</i> (n = 4; 25.0%) <i>E. faecalis</i> (n = 1; 6.3%)	1500 mg d1 + 500 mg d7, followed by 500 mg biweekly for 2 months (hip) or 3 months (knee) (n = 9; 56.3%) Other regimens (n = 7; 43.8%)	n = 11 (68.8%)	12/16 (75.0%)
Present study	Multicentric retrospective study PJI treated with dalbavancin (France)	n = 17	Polymicrobial (n = 5; 29.4%) MSSA (n = 9; 52.9%) MRSA (n = 1; 5.9%) Methicillin-susceptible CoNS (n = 6; 35.3%) MRSE (n = 4; 23.5%)	1500 mg d1 (n = 3; 17.6%) 1500 mg d1 + 1500 mg d7 (n = 8; 47.1%) Other regimens (n = 7; 41.2%)	n = 8 (47.1%)	8/17 (47.1%)

BJI, bone and joint infection; CoNS, coagulase-negative staphylococci; d, day; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MSSA, methicillin-susceptible *S. aureus*; N/A, not available; SSTI, skin and soft-tissue infection.

tion. Dalbavancin is an antibiotic active against Gram-positive cocci with a long half-life and in vitro biofilm activity. There are few studies in the literature on the use of dalbavancin during bone and joint infection, especially PJI [5,9–11], and only one focused solely on PJI [6]. Here we describe the specific use of dalbavancin in PJI among a previously published French cohort of dalbavancin use in real life.

In our cohort, clinical cure was achieved in 8/17 patients (47.1%), which is lower than usually reported, despite the low MICs

of bacteria involved regarding EUCAST breakpoints (0.125 mg/L for staphylococci) [12].

However, in our study, dalbavancin was mostly used in salvage condition and polymicrobial infections. Polymicrobial infections occurred in five cases, which might explain the low cure rate of our study. Indeed, polymicrobial infections during PJI are infrequent and are associated with poor prognosis [13,14]. Moreover, as in everyday practice, our patients were older, had numerous comorbidities and had already benefited from several antibiotic ther-

apies compared with previous studies, as in everyday practice. Although our sample size is small, our patients appeared more severe in the failure group, with one sepsis, one septic shock and one patient managed without surgery.

Also, Morata et al. reported a favourable outcome in 15/23 patients (65.2%) when the implant was retained and 16/21 (76.2%) when the implant was removed, suggesting the paramount importance of effective surgery [5]. It is of note that most of our patients were managed with DAIR.

Furthermore, in the literature review, we noted that CoNS (60.2%) were the most predominant pathogens, whereas in our study we noted one-half CoNS and one-half *S. aureus*.

Finally, in our study as well as in the literature, dalbavancin administration schemes were heterogeneous. The study plan of Rappo et al. regarding the use of dalbavancin in osteomyelitis included two doses of dalbavancin at a 1-week interval [3] and was the main represented scheme in our study, even if the dosing scheme varied.

The limits of our study and the review of the available data were the small number of patients and the heterogeneity of microbiology and dalbavancin use including administration regimen and dosage.

For all cases of PJI treated with dalbavancin available in the literature, the overall results were favourable in 68/93 cases (73.1%). Regardless of the dose, the treatment appears to be well tolerated as described in the literature [15].

5. Conclusions

Our study and literature data suggest that the use of dalbavancin in PJI could be considered, even in salvage therapy. Overall, dalbavancin appears to be a safe and easy treatment for the management of outpatients. We need more prospective studies and randomised clinical trials to confirm these preliminary results. Moreover, the prolonged treatment for PJI requires an optimisation of administration schedules. Pharmacological assays of residual concentrations would allow standardisation of practices.

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