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Efficacy and Safety of Dalbavancin Monotherapy as Salvage Treatment for Bone and Joint Infection

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Abstract: Bone and joint infection (BJI) treatment is challenging with significant morbidity and mortality. Dalbavancin is a semi-synthetic lipoglycopeptide analogue of the teicoplanin class that exhibits bactericidal activity and a long half-life. The use of dalbavancin may be an option in cases of gram-positive BJI. From November 2017 to April 2019, dalbavancin was used in monotherapy as a salvage option for BJI, as follows: 1500 mg, 1st (D1) and 8th (D8) days, repeated if needed. The follow-up period was of 6 months for osteomyelitis and 1 year for prosthetic joint infections (PJIs). The demographics of the 16 patients showed that 75% were men (n=12), with a mean age of 77.8 years [64-90]. The BJI characteristics: 5 cases of vertebral osteomyelitis; 12 cases of lower limb BJI {8 joint infections, among which were 6 PJIs (4 knees, 2 hips) and 4 cases of foot osteomyelitis)}; 2 cases of shoulder PJI. The debridement, antibiotics, irrigation, and implant retention (DAIR) procedure was performed in 83.4% (5/6) of cases. Monobacterial biopsy was obtained in 75% (n=12) of patients with majority of staphylococcus (15/25) dalbavancin susceptible micro-organismes): 14 Staphylococcus aureus (10/14 methicillin susceptible). Twelve patients received 2 doses of dalbavancin. The mean duration of the 1st antibiotherapy was 18.3 days [0-49]. The clinical success rate was 75% at the end of follow-up with no major side effects of dalbavancin. This report highlights the potential role and efficiency of dalbavancin in treating fragile patients who require long-term antimicrobial therapy with excellent tolerance profiles.

Keywords: Dalbavancin, Bone and Joint Infection, Prosthetic Joint Infections, Osteomyelitis

1. Introduction

Bone and joint infection (BJI) in the ageing population continues to be associated with significant morbidity and mortality. In France, as in other Western European countries, gram-positive BJIs are preponderant [16]. Staphylococcal BJI is the most frequent type and often is methicillin-resistant. Vancomycin is usually the "gold standard" antibiotic, and full treatment requires prolonged antibiotic therapy. Dalbavancin is a semisynthetic lipoglycopeptide analogue of the teicoplanin class that has bactericidal activity and a long half-life [8, 23]. Dalbavancin is approved for the treatment of skin and soft-tissue infections as an intravenous (i.v.) infusion of a single dose (1500 mg i.v.) or as two doses (1000 mg i.v. followed by 500 mg i.v. 7 days later) [24]. Nevertheless, the use of dalbavancin in BJI could be an option [2, 3, 4, 6, 9, 19, 22].

Rappo et al. [19] used dalbavancin for the first time in 2016 for osteomyelitis treatment in adult patients with a two dose regimen in a randomized clinical trial of efficacy and safety.

Dalbavancin was used by Bartoletti et al. in 2019 for the treatment of deep sternal wound infection [4] and Almangour

TA et al. showed good results in real life for a retrospective matched cohort study comparing the use of dalbavancin versus standard care for the treatment in osteomyelitis in 2020 [3].

The use of dalbavancin in the treatment of prosthetic joint infections (PJI) caused by different Gram-positive bacteria was published by Buzon et al. since 2019. In real life, the French national cohort of first use of dalbavancin highlights a high proportion of off-label use for this antibiotic [9] and especially for bone and joint infections and osteomyelitis. The extended-duration and sufficient distribution of dalbavancin into bone and articular tissue [10] place this antibiotic in an interesting position for BJI treatment. Matt M et al. showed good results in dalbavancin use for PJI in real life in a national cohort study [17], despite heterogeneous administration of dalbavancin doses. The aim of our study is to reinforce these results with the homogeneous administration of dalbavancin as a salvage treatment for BJI, in a very old population. The safety concerns of the use of dalbavancin in monotherapy for a population with several comorbidities and in failure of first or more lines of antibiotic treatment is also important in this study.

2. Materials/Methods

During November 2017 and April 2019, dalbavancin was used in monotherapy as a salvage option for BJI, as follows: 1500 mg, 1st (D1) and 8th (D8) days, repeated if needed [19]. The prospective clinical and biological follow-up was 6 months for osteomyelitis or BJI without a prosthesis and 1 year with a prosthesis (PJI). This cohort of patients is complementary to the "French national cohort of first use of dalbavancin [9] with patients treated before the opening and after the closure of the national register. Patients were informed that their clinical data could be used for research purposes after anonymization. This study was carried out in accordance with the World Medical Association Declaration of Helsinki. Data collected included patient demographics, underlying conditions, infection site, identification of different pathogens, source control of infection, antimicrobial therapy administered before dalbavancin, the principal reason for dalbavancin use, dalbavancin administration (unitary doses, number of doses), C reactive protein, adverse events, and clinical outcome. Dalbavancin minimum inhibitory concentrations (MICs) were determined by the ETEST®. Unfortunately, we did not have the dalbavancin plasmatic concentration dosing method at our disposition during the study.

3. Results

3.1. Demographics

During the eighteen months of prospective inclusion, 16 patients were treated in this study: 75.0% were men (n=12), with a median age of 77.8 years [64-90]. The most common underlying condition was renal failure in 68.8% (n=11), followed by diabetes mellitus in 37.5% (n=6) and atrial fibrillation in 37.5% (n=6) of cases. Lower limb arteriopathy was present in 31.2% (n=5) of cases. Three (18.8%) patients had a cardiac bioprosthesis. One patient had active neoplasia with chemotherapy.

3.2. The BJI Characteristic's

In half of the cases (n=8), PJI occurred secondary to health care (nosocomial infection). The patients presented the following conditions:

1) 5: vertebral osteomyelitis.
2) 12: lower-limb BJI.
3) 8: joint infection.
4) 6: PJI (4 knees, 2 hips).
5) 4: foot osteomyelitis.
6) 2: shoulder PJI.
7) 3 (18.7%) patients had two or more localizations of BJI.

3.3. Microbiology

In 75.0% (n=12) of cases, the biopsy was monobacterial. A total of 32 micro-organisms were identified in these biopsies, and 78.2% (n=25) were covered by the dalbavancin antimicrobial spectrum. The most common microorganism identified in BJI was *Staphylococcus aureus* in 56.0% of cases (10/25 MSSA, methicillin-susceptible *Staphylococcus aureus*, and 4/25 MRSA, methicillin-resistant *Staphylococcus aureus*), followed by *Enterococcus faecalis* (n=5), *Streptococcus spp*. (n=3), *Corynebacterium spp*. (n=2), and *coagulase-negative staphylococcus* (n=1). None of the polymicrobial BJIs were nosocomial infections. Minimum inhibitory concentration (MIC) by the ETEST® method was performed in all monobacterial BJIs (n=12). For the 25 dalbavancin susceptible micro-organisms, we could determine the MIC for 19 micro-organisms. The MIC median was 0.047 mg/l (0.004 – 0.125). For 3 *Staphylococcus aureus* isolates, the MIC was 0.125 mg/l (1 MRSA, 2 MSSA).

*3.4. Bacteremia, BJI and Infective Endocarditis: (*Duke Criteria for Infective Endocarditis, [13])*

In 68.8% (11/16) of BJIs, concomitant bacteraemia occurred with possible or certain infective endocarditis (IE*). In 27.3% (3/11) of cases, transoesophageal echocardiography or PET scans were positive for IE. For 6 patients (37.5%), bacteraemia was concomitant with a deep abscess, mostly in the psoas muscle and spleen in one case.

3.5. Surgical Treatment

No surgical intervention was needed for vertebral osteomyelitis. In all cases of foot osteomyelitis, the patient benefited from surgical debridement associated with transmetatarsal amputations if needed. For the PJI cases, the debridement, antibiotics, irrigation, and implant retention (DAIR) protocol were chosen after multi-disciplinary staff consultations in 83.4% of cases

(5/6). The median age of patients with DAIR was 84 years (66-90 years). No cardiac surgery was chosen after multi-disciplinary staff consultations with patient and family participation.

3.6. Medical Treatment

Dalbavancin was used as monotherapy to cover the spectrum of microorganisms, and other associated antibiotics (tazobactam-piperacillin or ceftazidime + levofloxacin) were needed in 2 polymicrobial BJIs. The majority of the patients (75.0%) received 2 doses of 1500 mg dalbavancin, D1 and D8, using the scheme of the Rappo 2018 study. In three cases (18.8%), 4 doses (D1, D8, D28 and D35) were necessary, with unitary doses adapted to renal function. One patient had only 1 dose. The mean duration of the initial scheme of antibiotherapy was 18.3 days [0-49]. Two patients had first-line dalbavancin, 75.0% (n=12) had a minimum of 7 days of previous antibiotics, 50.0% (n=8) had a minimum of 14 days, and 37.5% (n=6) had more than 30 days of previous antibiotics. The principal reasons for changing previous antibiotics for dalbavancin were as follows: poor tolerance to antibiotics in 50% (8/16), poor efficacy of the 1st antibiotherapy in 18.8% (3/16), poor compliance in 12.5% (2/16), preservation of quality of life with simplicity of administration and good tolerance (2/16) and relapse of infection (1/16) during chemotherapy and after 6 weeks of traditional bi-therapy in BJI, with simplification. Regarding antibiotherapy, all the patients appreciated the simplicity of administration and the good quality of life.

3.7. Outcomes and Success

The global clinical success rate was 75.0% (12/16) after one year of follow-up. The median age of these patients was 76.5 [66-90] years. We had 3 failures for 12 patients with monobacterial BJI (1 MSSA, 1 MRSA and 1 streptococcal case) and 1 failure for 4 patients with polymicrobial infection. The median age of these patients was 86.5 [64-89] years.

Of these 4 patients with treatment failure, 3 patients died (F 89 years, M 89 years, F 84 years), and one was cured after a switch to teicoplanin and rifampicin for 3 months (M 64 years). These case characteristics are described in *Table 1*.

A 4th patient died of her active neoplasia after the cure and the final monitoring consultation for hip BJI, psoas abscess and bacteremia caused by MSSA (F 66 years).

The success rate in foot and vertebral osteomyelitis was 75.0% (6/8).

The success rate in PJI was 66.6% (4/6).

The success rate when there was suspicion of endocarditis or a certain diagnosis (Duke criteria) was 63.6% (7/11).

The success rates in cases of monobacterial BJI were as follows: 83.3% (5/6) MSSA, 66.6% (2/3) MRSA, 1/1 Enterococcus faecalis, 1/1 Corynebacterium spp, and 0/1 Streptococcus spp.

The C-reactive protein (CRP) level became less than 5 mg/l in 56.3% of all patients (9/16) during antibiotic treatment and 37.5% (6/16) at 1 month of monitoring. The mean CRP level at 1 month was 35.8 mg/l, and the median was 17.7 mg/l (0.5 – 167).

Table 1. *Characteristics of failure cases.*

Sex, age	**F,89**	**M,89**	**F,84**	**M,64**
Microbiology	Streptococcus bovis	MSSA, Pseudomonas, Enterococcus faecalis, Clostridium perfringens	MSSA	MRSA
MIC	0.004	0.125	0.094	0.047 0.094 0.064
Infection	Hip PJI	Foot osteomyelitis	Knee PJI, 2 shoulder PJI, Psoas abscess	Vertebral osteomyelitis, Splenic abscess, Recurrent bacteraemia under dalbavancin
1st antibiotic	None	Ceftazidime + linezolid + levofloxacin	Cefazolin + levofloxacin	Vancomycin + clindamycin + Bactrim® (vancomycin => daptomycin)
Days of 1st antibiotic	0	5	30	12
Surgery	DAIR	Debridement and transmetatarsal amputation	Ablation of knee PJI, DAIR of 2 shoulder PJI	Percutaneous guided drainage or classical surgical of splenic abscess impossible.
Comorbidity	Aortic bioprothesis	Severe arteriopathy in the palliative stage for vascular surgery, extensive necrosis	Cachexia	Chronic prostatitis MRSA with urinary tract Catheter, Intellectual disability
Duke criteria	After 3 months of delay	yes	yes	yes
Dalbavancin	4 doses of 1500 mg	2 doses of 1500 mg (and ceftazidime for Pseudomonas, metronidazole for anaerobes)	1 dose of 1500 mg	4 doses of 1500 mg
Issue	Death	Death	Death	Success after switch to 6 weeks of teicoplanin + rifampicin

MSSA: methicillin-susceptible staphylococcus aureus, MRSA: methicillin-resistant Staphylococcus aureus, MIC: minimum inhibitory concentration, PJI: prosthetic joint infection, DAIR: debridement, antibiotics, irrigation, and implant retention.

Table 2. *Comparison of the cure rates in different studies and pathologies.*

Study	Cure rate				Median age (years)
	Global	Osteomyelitis	PJI	IE (Duke)	
Present study	75.0% (12/16)	75.0% (6/8)	66.6% (4/6)	63.6% (7/11)	77
Almangour 2020	-	100% (11/11)	-	-	50
Bouza 2018	84.1%	91.7%	80.0% (16/20)	85.7%	63
Buzon 2019	-	-	75.0% (12/16)	-	76
Dinh 2019	79.4% (54/68)	76.1% (34/46) all BJI		72.2% (13/18)	63
Matt 2021	-	-	47.1% (8/17)	-	69
Morata 2019	-	-	70.5% (31/44), 65.2% (15/23) if DAIR	-	64
Rappo 2019	-	97.0% (65/67)	-	-	49
Tobudic 2018	-	-	-	92.6% (25/27)	60
Tobudic 2019	63.8% (46/72)	55.8% (19/34)	37.5% (3/8)	-	56
Wunsch 2019	89.0% (90/101)	86.6% (26/30)	90.6% (29/32)	92.0% (23/25)	65

BJI: bone and joint infection, PJI: prosthetic joint infection, DAIR: debridement, antibiotics, irrigation, and implant retention, IE: infective endocarditis.

3.8. Tolerance to Dalbavancin

Excellent tolerance to dalbavancin was observed: there was one case of slight headache and one case of arterial hypotension after the first administration with no complementary medication needed. No intravascular catheter related bloodstream infection after dalbavancin administration was noted. There were no allergies, gastrointestinal symptoms or alterations in renal function. This is a relevant finding because of the numerous patients' comorbidities with renal impairment in an ageing population. Renal function was reestablished after the switching of vancomycin to dalbavancin in one patient. The global satisfaction of patients with the administration of and tolerance to dalbavancin was very good.

4. Discussion

The pharmacokinetic characteristics of dalbavancin, its long half-life of 15 days against gram-positive cocci [10, 15, 23], its interesting concentration in the articular synovium and bone tissue [10], and its in vitro activity on biofilms [14], make this molecule a possible solution for BJI treatment. An increasing number of studies have been published on the use of dalbavancin in real life, and the majority of these have been retrospective [2, 3, 6, 7, 9, 17, 18, 21, 25]. The only prospective study of dalbavancin use in adult osteomyelitis [19] presents an option for secondary treatment of BJI in difficult, salvage cases. This treatment schema (1500 mg D1, 1500 mg D8) was used in the present study before plasmatic dosing was available in France.

Often, BJI is associated with bacteremia, and gram-positive cocci may be implicated in IE. This situation requires prolonged, bactericidal antibiotic treatment, combined, if necessary, with surgery and always accompanied by infectious source control. Dalbavancin could be very useful in these complicated situations, for example, the good results shown by Tobudic et al. in their 2018 [20], retrospective study of dalbavancin as the primary treatment in gram-positive IE. The global success of dalbavancin monotherapy as salvage treatment in our study was 75.0% (12/16). The cured patients were 10 years younger than the patients with failure.

Table 2 compiles the rate success of different studies. In the real-life experience of Bouza, 2018 [6], the overall successful clinical outcome was 84.1%. However, if we compare our cohort with the Bouza cohort of patients in whom dalbavancin was administered as salvage therapy, we have a similar cure rate: 75.0% (12/16) vs 76.2% (16/21). Additionally, the patients in this cohort were much younger (nearly 20 years of age difference) than those in our cohort. There was less comorbidity: renal impairment 21.7% vs 68.8% and cardiovascular disease 31.9% vs 68.0% (atrial fibrillation, cardiac bioprosthesis, and lower limb arteriopathy). The length of previous antibiotherapy was comparable, with a median of 18 days. The dalbavancin administration was markedly different, with higher doses in our study (1500 mg per treatment vs 1500 mg D1 and D8, or more doses) with fewer adverse effects. In the French national cohort, Dinh [9] found a global outcome with a cure rate of 79.4% (54/68), which was comparable with our results but in a younger cohort (63.1 vs 77 years). Additionally, concomitant antibiotics were used with dalbavancin in 45.3% (34/75) of cases in the French national cohort, but only dalbavancin monotherapy was used in our study for the micro-organisms of the spectrum. In the Tobudic 2019 study [21], a 64% clinical cure rate was detected at the end of dalbavancin therapy without additional antibiotic therapy in a young population (56.5 years).

Osteomyelitis treatment success rate (including that for vertebral osteomyelitis) in the present study was 75.0% (6/8). This rate of cure was lower than the excellent result of 94.0% in the Rappo 2019 study [19]. The context is very different with treatment of acute osteomyelitis in a young population (mean age: 49 years), without the weight of comorbidity. The Almangour 2020 retrospective study [3] reported a perfect rate of cure (100%, n=11) for acute osteomyelitis treated with 3000 mg of dalbavancin in a young population (50 years). In our study, the characteristics of 2 osteomyelitis cases of failure were very different:

a) Vertebral osteomyelitis (M 64 years), complicated with persistent bacteremia, spleen abscess (CT-guided drainage impossible) and IE (echocardiographic vegetation after 1 month). After 4 doses of 1500 mg of dalbavancin, the patient was switched to teicoplanin and rifampicin for 6 weeks and was cured without cardiac surgery.

b) Foot osteomyelitis (M 89 years), polymicrobial, in a patient with palliative limb arteriopathy with extensive necrosis after 2 trans-metatarsal amputations.

Closer cure rates in a younger population were reached in the Tobudic et al., 2019 study [21], with 65.0% (13/20) success in cases of nonvertebral osteomyelitis and 50.0% (7/14) success in cases of vertebral osteomyelitis.

PJI: The success rate in our study was 66%, with a high rate of DAIR: 83.3% (5/6).

Our cure rate is similar to that in the Morata et al. 2019 study [18], where DAIR was applied in only 52.3% of 45 patients, with 65.2% (15/23) success. The cured proportion of the cases where implants were removed was higher: 76.2% (16/21).

Infective endocarditis (possible or certain after Duke criteria): The success rate was 63.6% (7/11) in our study.

The rate of success was higher in all previous retrospective studies but in younger cohorts:

1) 92.6% for the Tobudic, 2018 study [20]. Surgical treatment of IE was performed in 59.3% of patients (16/27, median age: 60 years vs 81 years). No surgical treatments were administered in our cohort.
2) 90% (n=25) for Wunsch, 2019 study [25]. There was no specification as to whether surgery was practised in these cases, and the median age was 65 years vs 81 years.
3) 85.7% (n=7) for Bouza, 2017 [6], with median age 63.5 years vs 81 years. Renal impairment was more significant in our cohort: 68.8% vs 27.5%.
4) 72.2% (n=19) in the retrospective French national cohort of Dinh, 2019 [9] but in a younger cohort (median age of 63 years vs 81 years).

The difference in success between monobacterial and polymicrobial infections was difficult to analyse in our study because of the limited number of patients.

Monitoring of the CRP levels is systematically performed in evaluations of BJI outcomes but, in our study, was not very useful regarding the values at the 1-month timepoint of the survey. We suspect that in this very ageing population, there were many reasons to have CRP > 5 mg/l.

The strengths of this study are its prospective management, long-term surveillance of patients, and utilization of dalbavancin for monotherapy in a geriatric population with preponderant comorbidity.

We also believe that in patients with biofilm-associated infections (PJI or chronic joint infection), source control is vital for treatment success. In the Tobudic et al., 2019 study [21], it was interesting to observe that in 87% of cases with clinical cure failure with dalbavancin, there was no clinical improvement with alternative antibiotics. Most likely, the high prevalence of diabetes mellitus is an important factor of failure, such as that involving incomplete source control.

However, in some geriatric populations with many comorbidities, the utilization of a bactericidal antibiotic with action on biofilms is interesting when we evaluate the balance benefit risk. Additionally, in situations where extended antibiotherapy is needed (i.e., in inoperable chronic PJI) or where clinical tolerance is important for long-term treatment, dalbavancin may offer a solution with sequential administration.

An interesting efficacy (71.0%, 15/21) has been reported in off-label treatment with dalbavancin in outpatient parenteral antibiotic therapy (OPAT) in vulnerable populations [5].

People who inject drugs and present bacteremia or IE are often perceived as having barriers to OPAT and standard daily administered antibiotics. In the Ajaka et al., 2020 study [1], initiating off-label use of dalbavancin in this population permitted a cure of 44.0% at D90 of follow-up.

5. Conclusion

Using dalbavancin in monotherapy in salvage situations to treat complex infections such as BJI, with or without implants, is a current option with interesting efficiency. The higher cure rate was found in foot and vertebral osteomyelitis. The cure rate decreases with the presence of bacteremia and infective endocarditis, the presence of joint prosthesis and DAIR use. This antibiotic is well tolerated even in a geriatric population with renal comorbidities. The next step is the realization of homogeneous prospective studies of the use of dalbavancin as monotherapy to cure complex infections such as BJIs associated with optimal surgical treatment in PJIs.

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