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Proceeding Paper

Experience of Real-Life Use of Dalbavancin as an Off-Label Treatment of Complicated Infectious Diseases in a Tertiary Care Hospital †

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Abstract: Dalbavancin is a lipoglycopeptide indicated for the treatment of acute bacterial skin and skin structure infections. The aim of this study is to describe the cases in which dalbavancin has been used as an off-label use for the treatment of infections by gram-positive microorganisms. Methods: we carried out a case report series study of all patients treated with dalbavancin as off-label from January 2017 to March 2022. Results: Dalbavancin was administered to seventeen patients. The most frequent diagnosis was osteoarticular infection in 52.94%of patients. The principal isolated microorganism was *Staphylococcus epidermidis* (47.00%). The posology of dalbavancin was highly variable and the median number of days of treatment was 14 (1–56). At 3 months of treatment only 2 patient died for others reasons and no patient had reinfection. Conclusion: dalbavancin is an antibiotic with a novel dosage in infectious diseases of Gram-positive that proven to be high effective because no patient manifested symptoms of reinfection.

Keywords: dalbavancin; off-label; posology

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1. Introduction

Dalbavancin is a lipoglycopeptide antibiotic whose mechanism of action involves disruption of cell wall synthesis by binding to the D-alanyl-D-alanine end of the peptidoglycan structure in the forming cell wall, preventing cross-linking (transpeptidation and transglycosylation) of disaccharide subunits, resulting in bacterial cell death. It is active against gram-positive microorganisms, including different species of multiresistant microorganisms such as *methicillin-resistant Staphylococcus aureus (MRSA)*. It is indicated for the treatment of acute bacterial infections of the skin and skin soft tissues in adults.

The most relevant pharmacokinetic feature is its prolonged action (half-life 14.40 days), which allows the administration of a single dose of 1500 mg or the administration of two doses of 1000 mg and 500 mg separated by 1 week, according to the data sheet.

Dalbavancin is usually used off-label, as it has a powerful activity against gram-positive pathogens that cause bone and joint infections (osteomyelitis), bacteraemias and endocarditis, among others. Which are infections that require long-term antibiotic therapy and long periods of hospitalization. Its prolonged action allows early discharge of hospi-

talized patients who require prolonged intravenous antibiotic therapy. Avoiding prolonged hospitalization and the risk of acquiring healthcare-associated infections, favoring home treatment and, at the same time, ensuring adherence to treatment.

The objective of this study is to describe the cases in which dalbavancin has been used as an off-label use for the treatment of infections by gram-positive microorganisms in a tertiary hospital.

2. Methods

Case report series study of all patients treated with dalbavancin as off-label use from January 2017 to March 2022.

Demographic, clinical and pharmacotherapeutic variables were considered: age, sex, justification for the request as off-label, diagnosis, microorganism, location of the infection, previous antibiotic treatment, dalbavancin dosing, duration of treatment, concomitant antibiotic treatment and follow-up of the patients at 3 months.

Data were collected from the electronic medical record and the electronic prescribing program.

3. Results and Discussion

The study included a total of nineteen patients for whom off–label dalbavancin was request to the pharmacy service. Two patients were excluded: one of whom died before administration of dalbavancin, and the other patient was proposed to discontinue the drug that interacted with another effective antibiotic during treatment.

Dalbavancin was administered to seventeen patients (Table 1) with a median age of 76 (33–99) years, 64.70% of whom were men. The justification for off-label use was in all patients the early discharge and the impossibility of treatment with other oral antibiotics due to interactions, microbial resistance, adverse effects and/or severity. All patients were tested for the sensitivity of dalbavancin.

Table 1. Results of: diagnosis, isolated microorganism, location and posology of our patients. MRSA: methicillin-resistant Staphylococcus aureus; MSSA: methicillin-sensitive Staphylococcus aureus.

	Diagnostic	Microorganism	Location	Dalbavancin Dosage
1	Bacteraemia	*Staphylococcus epidermidis*	Joint fluid	2 doses of 1500 mg biweekly
2	Osteoarticular infection	*MRSA*	Joint fluid	1 dose of 1500 mg + 1000 mg biweekly
3	Osteoarticular infection	*Staphylococcus epidermidis*	Abscess	1 dose of 1500 mg + 1000 mg biweekly
4	Bacteraemia	*Staphylococcus epidermidis*	Blood culture	1 dose of 1500 mg + 1000 mg biweekly
5	Bacteraemia	*MRSA*	Blood culture	1 dose of 1500 mg + 1000 mg biweekly
6	Osteoarticular infection	*Staphylococcus epidermidis*	Osteosynthesis	2 doses of 1500 mg biweekly
7	Bacteraemia	*Staphylococcus warneri*	Blood culture	Single dose of 1500 mg
8	Endocarditis	*MSSA*	Ulcer	1 dose of 750 mg + 375 mg weekly
9	Osteoarticular infection	*MRSA*	Abscess	1 dose of 750 mg + 375 mg weekly
10	Osteoarticular infection	*MSSA*	Osteosynthesis	1 dose of 1500 mg + 500 mg weekly
11	Bacteraemia	*MSSA*	Blood culture	Single dose of 1500 mg
12	Osteoarticular infection	*Staphylococcus epidermidis*	Joint fluid	2 doses of 1500 mg biweekly

13	Endocarditis	*Staphylococus haemolyticus*	Blood culture	1 dose of 1000 mg + 500 mg at two weeks
14	Osteoarticular infection	*MSSA*	Blood culture	1 dose of 1000 mg + 500 mg at two weeks
15	Endocarditis	*Staphylococcus epidermidis*	Blood culture	1 dose of 1000 mg + 500 mg at two weeks
16	Osteoarticular infection	*Staphylococcus epidermidis*	Osteosynthesis	1 dose of 1000 mg + 500 mg at two weeks
17	Osteoarticular infection	*Staphylococcus epidermidis*	Osteosynthesis	1 dose of 1000 mg + 500 mg at two weeks

The most frequent diagnosis were osteoarticular infection in 52.94% of patients, followed by bacteremia in 29.40%, and endocarditis in 11.76%. The isolated microorganism was *Staphylococcus epidermidis* (47.00%), *methicillin-resistant Staphylococcus aureus* (17.65%), *methicillin-sensitive Staphylococcus aureus* (23.53%), *Staphylococcus haemolyticus* (5.89%) and *Staphylococcus warneri* (5.89%). Microorganisms´ isolation: 33% blood culture, 25% joint fluid, 16.67% abscess, 16.67% osteosynthesis and 8.33% ulcer.

All patients were treated with other antibiotics before starting dalbavancin. Previous antibiotic treatment were daptomycin in 13 patients (76.47%) (9 of them also received other antibiotics before), linezolid in 3 patients (17.65%) (2 of them also received other antibiotics before) and others in 2 patients (11.76%).

Dalbavancin dosing was highly variable: 2 doses of 1500 mg biweekly (17.65%; n = 3), 1 dose of 1000 mg + 500 mg at two weeks (29.41%; n = 5), 1 dose of 1500 mg + 1000 mg biweekly (23.53%; n = 4), single dose of 1500 mg (11.76%; n = 2), 1 dose of 750 mg+ 375 mg weekly (11.76%; n = 2) and 1 dose of 1500 mg + 500 mg weekly (5.89%; n = 1).

The median number of days of treatment was 14 (1–56). Concomitant oral antibiotics were used in 29.41%: rifampicin(n = 5) and levofloxacin(n = 2). After 3 months of treatment only 2 patient died for others reasons and no patient presented reinfection.

Our hospital's use of dalbavancin largely is similar to other hospitals in real-life situations.

A recently published systematic review (2020), which included 38 studies (18 randomised controlled trials/case series and 20 case reports) on the use of dalbavancin and oritavancin in indications other than acute bacterial skin and soft tissue infections, showed a success rate of 73% for osteoarticular infection (most common indication), 68% for endocarditis and cardiac device-related infections and 75% for catheter-related infections.

In a multicentre retrospective study including 101 patients receiving dalbavancin from September 2016 to March 2018, the infections treated were prosthetic joint infection (31%), osteomyelitis (29%), endocarditis (25%) and acute bacterial skin and soft tissue infections (12%). Sixty-three per cent of patients received other antibiotics concomitantly. The total cumulative mean dose of dalbavancin was 3,357 mg (±2283 mg). Outcomes and tolerability were measured at 90 days, with a clinical success rate of 89%. Side effects occurred in 3/101 patients.

Furthermore, in a retrospective observational study conducted in a hospital in our setting, which included 102 patients treated with dalbavancin (69.6% off label) from October 2016 to August 2019, 89 patients (93.7%) had clinical and microbiological resolution of infection at the end of the study. The most frequent indications were: catheter-related bacteraemia (15.7%) and endocarditis (13.6%). The main reason for switching to dalbavancin was early patient discharge (79.4%, n = 81). The median reduction in length of hospital stay was 14 days per patient, with an estimated saving of about 4550 euros per patient. In addition, a trend towards a significant improvement in quality of life outcomes with dalbavancin has been observed. Outpatients reported significantly higher comfort and satisfaction.

4. Conclusions

Dalbavancin is an antibiotic with a novel dosing in gram-positive infectious diseases such as endocarditis and osteomyelitis that require long periods of treatment, due to its pharmacokinetic characteristics. Its main contribution in our setting has been to allow earlier hospital discharge in patients who did not have oral alternatives and the only reason for hospitalization was the need for intravenous antibiotic treatment.

In this study we observed several cases of off-label dalbavancin use in a tertiary hospital. Most of our patients achieved clinical success, with resolution of the infection and no relapses occurred in the 3-month follow-up period after finishing treatment. The two patients who died in our study died from other reasons than the cause that motivated the prescription of dalbavancin.

Our results show the potential use of dalbavancin extends beyond the authorized indication in clinical practice as it has been shown to be highly effective as no patient manifested symptoms of reinfection.

For these reasons, we have developed a protocol in our hospital for the use of dalbavancin as an off-label treatment in severe gram-positive infections. Its use is restricted to patients who meet all of the following situations:

- Severe and/or complex infections caused by gram-positive microorganisms sensitive to dalbavancin (treatment directed by Microbiology results).
- When they require prolonged antibiotic treatment (≥2 weeks).
- When linezolid is contraindicated due to risk of developing—serotonin syndrome when prescribed with antidepressants (serotonin reuptake inhibitors, tricyclic antidepressants) or due to high risk of toxicity with this drug due to renal failure (creatinine clearance (CrCl) < 30 mL/min) and/or alteration of the previous haemogram.

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