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Real-world use of telavancin in the treatment of osteomyelitis

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ABSTRACT

This is a retrospective analysis of patients with osteomyelitis who received telavancin at some time during their treatment course. The primary outcome was the percent of patients cured or improved at the end of telavancin therapy (EOTT). The secondary outcome was the percent of patients cured or improved three months after discontinuation of telavancin therapy. There were 32 cases of osteomyelitis with methicillin-resistant Staphylococcus aureus identified in 17 (56.7%), methicillin-sensitive Staphylococcus aureus 2(6.6%), coagulase negative staphylococci 6 (20.0%) and other pathogens, 5 (16.7%). At EOTT, 87.5% of patients had their osteomyelitis cured and 94.6% had the infection cured at three months after telavancin was completed. The most common adverse events associated with telavancin were gastrointestinal in nature (nausea (25.8%), vomiting (9.7%) and diarrhea (3.2%)) followed by metallic taste (6.5%). A favorable outcome was achieved for many patients receiving the antimicrobial regimen that included telavancin for the treatment of osteomyelitis.

Osteomyelitis is one of the most challenging infections for the infectious disease clinician to manage (Lew and Waldvogel, 2004). Treatment considerations involve antimicrobial selection, dosing, routes of administration and surgical management. It has been well established that late relapses may occur even after perceived successful antibiotic therapy. This may occur in the range of 20–30% and does not appear to be related to a specific pathogen (Garcia del Pozo et al., 2018). In a series of 116 patients with osteomyelitis followed for more than 1 year after discharge, relapses occurred in 26 patients at a mean of 11.2 months (Garcia Del Pozo et al., 2018). In a recent publication of 1003 patients with osteomyelitis treated in Europe *S. aureus* was the most common pathogen occurring 37.7% of cases (Li et al., 2019) In addition, the frequent occurrence of methicillin-resistant *S. aureus* (MRSA) as a pathogen in osteomyelitis emphasizes the need for additional antimicrobial agents with activity against this pathogen (Harting et al., 2017; Lamp et al., 2007). Clinicians are challenged to find optimal treatment strategies for *S. aureus* infections that will either enhance or serve as an alternative to available anti-staphylococcal therapies.

With high rates of MRSA infections occurring in many regions, clinicians cannot rely on beta-lactams except for ceftaroline as initial empiric therapy for *S. aureus* infections or specific therapy when MRSA is the identified pathogen. MRSA infections accounted for 10.08 discharges per million patients versus MSSA, which accounted for 7.27 discharges per million patients for all *S. aureus* infection-related hospitalizations in the year 2014. (Klein et al., 2017). In addition, the development of *S. aureus* strains with reduced susceptibility to vancomycin, vancomycin-intermediate and -resistant strains, and daptomycin non-susceptible strains pose additional challenges for the practicing clinician. The prevalence of VISA was 7.93% between 2010 and 2014 (Zhang et al., 2015) and the daptomycin non-susceptibility has been reported occasionally from deep-seated infections but most recently increasing rates of daptomycin non-susceptible strains have been identified in either the skin or anterior nares of patients with atopic dermatitis. The rate of non-susceptibility was 23.4% when identified by E test (Blazewicz et al., 2017).

Fortunately, VRSA strains are very uncommon, having been reported in only 14 cases to date (McGuinness et al., 2017). The rationale for telavancin as an alternative treatment option is its excellent *in vitro* activity against MRSA and the emergence of less susceptible strains to available agents such as vancomycin and daptomycin (Karlowsky et al., 2015). In addition, telavancin has shown good antimicrobial activity against staphylococcal biofilms and superior efficacy compared with vancomycin against MRSA strains causing biofilms. Telavancin also inhibits the formation of biofilms at concentrations below each isolate's respective minimal inhibitory concentration (MIC) (Gander et al.,

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2005). Thus, the identification of telavancin as a treatment option for serious infections such as osteomyelitis is important in expanding the clinicians' choices in treatment.

Telavancin, a semi-synthetic derivative of vancomycin, exhibits concentration-dependent bactericidal activity via a dual mechanism of action involving inhibition of bacterial cell wall synthesis as well as disruption of cell membranes (Higgins et al., 2005)). It has broad anti-staphylococcal activity, including activity against isolates with methicillin-resistance, and intermediate vancomycin susceptibility, (Karlowsky et al., 2015). Telavancin has been approved in the United States and Canada for the treatment of adult patients with complicated skin and skin structure infections (cSSSI) due to susceptible Gram–positive organisms based on two identical double-blind, randomized, active-controlled multinational studies (ATLAS 1 and 2) (Stryjewski et al., 2008; Anon, 2014). Additionally, based on results from two identical double-blind, randomized, active-controlled, multinational studies (ATTAIN 1 and 2) (Rubinstein et al., 2011), telavancin received approval for the treatment of hospital -acquired and ventilator-associated bacterial pneumonia due to susceptible isolates of *S. aureus* when alternative agents are not appropriate (Anon, 2014).

There have been some published reports indicating clinical improvement in patients with osteomyelitis treated with telavancin, Schroeder et al., 2018, Peyrani et al., 2012, Twilla et al., 2011, Xu et al., 2015). Our retrospective review was designed to capture clinical practice information on the use of telavancin in the treatment of osteomyelitis. This approach is similar to what has been used in other published retrospective case series and accepted for describing the experience with other anti-staphylococcal agents such as daptomycin use in the treatment of osteomyelitis (Rolston et al., 2007, Lamp et al., 2007). The primary objective of this study was to retrospectively determine clinical outcomes of patients treated with telavancin as part of their antimicrobial therapy in a post-marketing, real world evaluation. This paper describes the results as a case series for patients treated with telavancin for osteomyelitis.

1. Materials and methods

1.1. Objective

To retrospectively review the outcomes of an antimicrobial regimen that included telavancin treatment of osteomyelitis during the post-marketing era (2010-2012), using a multi-site case series approach.

1.2. Primary outcome

The percent of patients cured or improved at the end of telavancin treatment (EOTT).

1.3. Secondary outcome

The percent of patients cured or improved on follow–up at 90 (±30) days after discontinuation of telavancin therapy.

1.4. Inclusion Criteria

This multicenter case series included six medical centers in the United States: Ascension-St John Hospital, Detroit, Michigan; the University of Tennessee, Memphis, Tennessee; Geographic Medicine Services of Biloxi, Mississippi; the Alabama Infectious Diseases Center, Huntsville, Alabama; AtlantiCare Regional Medical Center, Pomona, New Jersey; and North Texas Disease Consultants, Dallas Texas. Male and non-pregnant females 18 years of age and older who received telavancin for any duration for the treatment of osteomyelitis and who were treated from 2010 to 2012 were included. A decision to use telavancin was not dictated by the protocol but at the discretion of the treating clinician. Furthermore, overall medical management was carried out at the discretion of the infectious disease physician and their medical team members.

Institutional review board approval was obtained by the Ascension St John Hospital Institutional Review Board. Medical records were abstracted using a standardized case report form (CRF). If data for the secondary outcome (90-day outcomes) were not available, patients were contacted by phone. All calls were made by the treating physician or research staff and verbal consent was obtained at the start of the phone call.

1.5. Data collection

Data were collected on demographics, comorbidities, clinical and laboratory findings, radiologic findings, pathology, microbiology, site of infection, antibiotic use, adverse events, safety and outcomes. Standardized case report forms were used to collect demographic and clinical information on all patients treated with telavancin. The osteomyelitis was categorized as acute if there were less than 30 days of signs and symptoms or chronic if it was longer. The site of infection was defined by the investigators according to clinical signs and imaging results. Infections were classified as hematogenous and were noted if the patient had endocarditis or associated line infection or they were classified as contiguous in association with diabetic foot ulcer, surgical wound infection, prosthetic joint infections or trauma. Patients' associated comorbidities such as diabetes mellitus, renal failure, prior orthopedic surgery, and immunosuppression were recorded as documented within the medical record. Adverse events, such as abnormal laboratory testing, were reported as abnormal based on criteria used in clinical practice at the respective institutions and was not protocol-driven.

1.6. Evaluation

The effectiveness of telavancin for osteomyelitis was determined based on clinical response as evaluated by the primary site investigator at the end of telavancin therapy (primary endpoint), at 30 days and at a follow-up visit at least 90 (± 30) days following the end of telavancin therapy (secondary outcome). Patients were categorized as cured, cured but requiring continued antimicrobial therapy, failed, or died. The criteria for evaluation were similar to criteria used in previous registry trials (Lamp et al., 2007).

Patients were considered cured, if they had resolution of clinical signs and symptoms. Patients were considered cured with continuation of antibiotic suppressive therapy if they had improvements in their clinical signs and symptoms but the clinician elected to continue antibiotic therapy other than telavancin that was felt to be needed for an appropriate duration for osteomyelitis. Patients were categorized as failures if they had any of the following: 1. inadequate response to therapy, 2. clinical worsening with new or recurrent signs and symptoms, 3. a need to change parenteral antibiotic therapy because of an adverse antimicrobial event or 4. a positive blood culture at the end of therapy. All CRFs were reviewed by the principal investigator.

1.7. Data analysis

As this was a case series, we included all cases who met the inclusion criteria at the participating sites. No formal sample size calculation was done. Descriptive statistics were generated to characterize the study population with respect to demographics and clinical variables. Continuous variables were summarized using the mean and standard deviation or median (minimum, 25th %ile, 75th %ile, maximum).

Categorical variables were summarized using frequency distributions. Comparisons of clinical outcomes by age, renal function or other continuous variables were compared using Student's *t*-test, the Mann–Whitney *U* test, ANOVA, or the Kruskal-Wallis test, as applicable. Comparison of success and failure by categorical variables were completed

using chi-squared analysis. All data were analyzed using SPSS v. 25.0. A *P* of 0.05 or less was considered statistically significant.

2. Results

Results of the study are summarized in Tables 1-5 and Fig. 1. Thirty-two patients treated at six medical centers were enrolled in the study. The demographic and clinical features of these patients are described in Table 1. Common patient characteristics included prior orthopedic surgery, diabetes mellitus and tobacco use.

The pathogenesis of infection was considered hematogenous in five cases and contiguous in 27 cases. Most infections were considered acute, 56.3% (18/32) and infections occurred at prior sites of surgery in 75% (24/32) of the cases. There were five patients who had prosthetic devices, four prosthetic knees and one prosthetic hip.

The pathogens recovered are indicated in Table 2 and included MRSA 56.7%, MSSA 6.6%, coagulase-negative *staphylococci* 20.0%, *Streptococcus agalactiae* 3.3%, mixed infection 10%, and *Propionibacterium species* 3.3%. All Gram-positive isolates recovered were vancomycin- and telavancin-susceptible.

The clinical outcomes at end of therapy, 30 days post therapy and 90 days post telavancin therapy are summarized in Fig. 1 and treatment failure/relapse occurred at 9.4%, 6.5%, and 6.5%, respectively. There was only one death and it was not associated with infection. This case was excluded from further analysis. Patients were not excluded if they were a failure at 30 days because subsequent therapy may have resulted in cure, but this was uncommon. There was one patient who was considered a failure at 30 days and cured at 90 days after receiving other antimicrobial therapy and one that had resolution of clinical signs and symptoms at 30 days who had a recurrence of signs and symptoms at 90 days and thus was considered a failure.

There were nine patients who received only telavancin for a mean of 36 ± 13.0 days (median: 42 days, range 13–47, IQR: 22.5, 46.5). Among the nine patients who received telavancin only as their therapy for osteomyelitis, seven were considered cured at the EOTT, 30 and 90-month day follow-up. One patient was considered cured at 0 and 30 days but had a relapse at 90 days and was considered a treatment failure. This patient's treatment failure was due to experiencing a rise in serum creatinine necessitating a change in antimicrobial therapy at the discretion of the treating clinician. Another patient with advanced cardiomyopathy had a cardiac arrest after 7 days of therapy and was switched to a different antimicrobial regimen at the discretion of the clinician. This patient was also deemed a clinical failure and required antibiotic therapy for the next 3 months with regimens including vancomycin meropenem, and levofloxacin. Thus, both treatment failures were due to adverse events described above.

The mean duration of telavancin therapy was 33.6 ±19.7 days for all patients (median: 31.5, range 6–94, IQR: 15, 47). The mean duration of therapy for all antibiotics was 111.0 ±107.9 days (median: 84, range 25–606, IQR: 49.5, 128.75). Most patients (62.5%) received antibiotic therapy after telavancin was stopped for a median of 32.5 days (range: 5-530, IQR: 17.75, 88.0). As this was a retrospective observational study, the decision to continue antibiotics after telavancin was stopped was at the discretion of the treating physician who felt that the osteomyelitis needed continued antibiotic therapy. Antibiotics given prior to and after telavancin therapy was stopped are summarized in Table 3. The mean percent of all antibiotic days that were telavancin was 40.8% ± 24.6%. Among patients who received other antibiotics

Table 1
Demographics and baseline clinical characteristics.

Characteristic	Mean ± S.D., Median (range) or Percent (n) (n=32)
Age	57.9 ± 17.0
Median LOS (days)	7.0 (0-49)
% Male	62.5% (20)
Comorbid conditions	
Diabetes mellitus	43.8% (14)
Renal failure	6.3% (2)
Tobacco abuse	21.9% (7)
Immunosuppression	9.4% (3)
Prior orthopedic surgery	71.9% (23)
Local features and pathogenesis	
Previous surgery	75% (24)
Foreign body	15.6% (5)
Trauma/fracture	31.3% (10)
Non-healing ulcer	12.5% (4)
Peripheral vascular disease	12.5% (4)
Neuropathy	12.5% (4)
Hematogenous	
Endocarditis	6.3% (2)
Line infection	9.4% (3)
Contiguous	
Diabetic foot ulcer	12.5% (4)
Surgical wound infection	6.3% (2)
Prosthetic joint infection	15.6% (5)
Orthopedic device other than prosthesis	15.6% (5)
Trauma	25.0% (8)
Other contiguous sources	6.3% (2)
Anatomical site of infection	
Femur	9.4% (3)
Tibia	15.6% (5)
Upper extremity	3.1% (1)
Pelvis	6.3% (2)
Thoracic vertebrae	12.5% (4)
Lumbar vertebrae	15.6% (5)
Foot	25.0% (8)
Hand	3.1% (1)
Type	
Acute (≪30 d of signs and symptoms)	56.3% (18)
Chronic	34.4% (11)
Unknown	9.4% (3)

Table 2
Microbiology results if positive.

Pathogen	Percent (n) n=30
MRSA	56.7% (17)
Coagulase negative *staphylococci*/ *S. epidermidis*	20.0% (6)
Streptococcus agalactiae	3.3% (1)
Corynebacterium spp and *Streptococcus viridans*	3.3% (1)
M. morganii; E. faecalis	3.3% (1)
MSSA	6.6% (2)
Gram-negative rods and Gram-positive cocci	3.3% (1)
Propionibacterium species	3.3% (1)

Table 3
Antibiotics administered before and after intravenous telavancin therapy.

Antibiotics	N (before, after)	Median duration(range) days before/after (days)
Cefazolin/cephalexin	4,1	2(1,7)/12
Moxifloxacin/levofloxacin	2,4	32 (6,58)/(9.161)
TMP/SMX	4,6	8 (2,14)/74(14,528)
Amoxicillin/clavulanic acid	0,2	0/14*
Clindamycin	6,0	15.5 (4,62)/0
Doxycycline	2,4	14 for both/22(13,59)
Ertapenem	6,4	4.5 (3,5)/12(1,34)
Metronidazole	1,0	7/0
Piperacillin/Tazobactam	4,0	2.5 (1,6)/0
Vancomycin	18,4	4 (1,47)/12.5(3,27)
Cefepime	0,2	0/22(1,43)
Daptomycin	6,5	7.5 (2,18)/21(18,43)
Meropenem	2,3	2 (1,3)/6(1,8)
Oxacillin	2,0	2/0
Rifampin	1,0	Not reported/0
Ciprofloxacin	0,2	0/16.5(3,20)
Linezolid	2,2	16 (14,18)/61.5(48,75)
Doripenem	1,0	6/0

* Only one of the two patients had duration reported.

Table 4
Clinical outcomes by pathogenesis.

Source	n	End of treatment		30 days		90 days ± 1 month	
		Cured	Treatment failure	Cured	Treatment failure	Cured	Treatment failure
Diabetic foot	4	75% (3)	25% (1)	100% (4)	0% (0)	50% (2)	50% (2)
Prosthetic joint/device	5	80% (4)	20% (1)	100% (5)	0% (0)	100% (5)	0% (0)
Vertebral osteomyelitis	9	88.9% (8)	11.1% (1)	100%% (9)	0% (0)	100% (9)	0% (0)
Trauma	8	75% (6)	25% (2)	75% (6)	25% (2)	100% (8)	0% (0)
Bacteremia	11	100% (11)	0% (0)	100% (11)	0% (0)	100% (11)	0% (0)

during telavancin therapy, the drugs given were meropenem (2), ertapenem (6), rifampin (3), and clindamycin (1).

The dose of telavancin therapy administered was 10mg/kg/day. Dose adjustments occurred based upon renal function with modifications occurring based upon recommendations from the package insert.

Clinical outcomes by pathogenesis are described in Table 4. Although the numbers are small in each of these groups, trauma patients had higher failure rates at 30 days and patients with diabetic foot infections had higher treatment failure rates at 90 days than patients with infections at other sites. While we did evaluate the inflluence of duration of telavancin therapy on clinical outcome, no correlation between these variables was found.

Adverse events from telavancin are described in Table 5. The attribution of the adverse event to telavancin was investigator assessment and not protocol driven. The most frequently reported adverse events were nausea (25.8%) and anemia (21.9%) as defined by the normal range within their reference laboratory at the respective institutions, followed by vomiting (9.7%). The mean serum creatinine on initiation of telavancin therapy was 1.0 ± 0.6 and the maximum serum creatinine was 1.3 ± 0.8mg/dl. The mean final serum creatinine was 1.12 ± 0.9mg/dl. Two patients (6.7%) had a change in serum creatinine of greater than twice baseline or decrease in the eGFR by 50% leading to discontinuation of telavancin.

3. Discussion

In this study of 32 patients with osteomyelitis, we found that patients who received telavancin at the recommended dose of 10 mg/kg once per day along with other antibiotics had their infection cured in 93.6% when evaluated at three months after the telavancin therapy was stopped. This suggests a similar outcome to what has been reported as the clinical experience in patients with osteomyelitis treated with other agents such as daptomycin (Lamp et al., 2007)

Our study included a very heterogeneous population with patients who had a variety of systemic and local compromising conditions as well as a variety of types of osteomyelitis infections including diabetic foot ulcers, prosthetic joint, orthopedic device related infections, trauma, and post-surgical wound infections. These are the types of patients who reflect the conditions arising in both the community as well as a university hospital setting. We noticed a higher failure rate among diabetics than among nondiabetics also which would possibly be related to the polymicrobial infection with anaerobes and/or Gram-negative rods that may not have been identified on culture techniques used by the clinicians. Furthermore, these patients also have some local compromising features such as poor vascularity which would delay clinical response and healing. MRSA was the most common organism isolated from these infections.

Table 5
Adverse events.

Adverse Event	Percent (n)
Nausea	25.8% (8/31)
Anemia of chronic disease	21.9% (7/31)
Vomiting	9.7% (3/31)
Metallic taste	6.5% (2/31)
Diarrhea	3.2% (1/31)
Infusion reaction	3.2% (1/31)
Pruritus	3.2% (1/31)
Red ,man syndrome	3.2% (1/31)
AST or ALT greater than 3 times upper limit of normal	3.1% (1/30)
Serum creatinine increase of 2 times baseline or eGFR decrease of 50 percent	6.3% (2/30)
Therapy changed because of maximum serum creatinine	6.3% (2/30)

The Infectious Diseases Society of America's guidelines recommends the use of beta-lactams for the treatment of methicillin-sensitive *S. aureus* infections, and all but two infections caused by *S. aureus* were methicillin resistant in this case series (Liu et al., 2011).

Our study did not reveal any adverse events that have not already been reported and recognized from controlled clinical trials of telavancin. There was however a higher rate of anemia. We are unable to attribute this to telavancin as many patients had trauma, frequent surgery, or anemia of chronic disease as reflected in Tables 1 and 5. Furthermore, reporting of anemia was left to the discretion of the treating clinician in terms of deviations from established laboratory values within each institution. The data collection did not require serial hemoglobin measurements to discern the change from baseline.

To date, there is a paucity of data regarding telavancin for the treatment of osteomyelitis. In a rabbit model of osteomyelitis, telavancin sterilized tibial MRSA infections with a success rate similar to vancomycin and linezolid (Yin et al., 2009). A retrospective case series of 14 patients found that in the 78% of patients that had an end of treatment outcome available, the clinical success rate was 91% (Harting et al., 2017). This study had nine patients who had a 30-day clinical success evaluation and a 12-month clinical success evaluation. In contrast, in our study, 31 patients had a follow-up 30 day after completion of telavancin and 23 had a follow-up after 90 days. There are other case reports or small case series describing the use of telavancin for the treatment of osteomyelitis (Peyrani et al., 2012; Schroeder et al., 2018; Twilla et al., 2011; Xu et al., 2015). These reports were of a smaller numbers of cases than the series reported in this article. The recognized limitation of our study is that patients received a mean duration of telavancin of 33.6 ±19.7 days and a median of 31.5 days. Although this exceeds the duration many patients would receive for acute osteomyelitis, the presence of concomitant antibiotics limits our abilities to attribute clinical outcome to therapy with telavancin. In a recent study, antibiotics were continued beyond 6 weeks for osteomyelitis for 76.7% of the 1049 participants, with a median total duration of therapy of 78 days in the intravenous group and 71 days in the oral group (Li et al., 2019). This prolonged administration of antibiotics is common in the management of this serious infection with various combinations of both oral and parenteral agents being used.

There are several strengths to our study. First, we collected data on drug tolerability and the occurrence of renal events. There were two cases of telavancin discontinuation due to renal events. The study included a follow up at three months after the telavancin was discontinued. In addition, the study provided a mix of patients that reflect the real world clinical practice of infectious diseases. Finally, this is the largest case series published to date of osteomyelitis for which telavancin was included in the therapy.

There are also limitations to this type of study. First, patients often received other antibiotics in addition to telavancin making determination of the efficacy of telavancin by itself and outcomes not possible. Our intention in this study was to share how telavancin is being used in the treatment of osteomyelitis. Second, follow-up was only for 90 days after the EOT with telavancin. Longer follow-up may have identified additional cases of relapse. In addition, our follow-up occurred at 90 days after telavancin was discontinued while other antibiotics may have been continued. This was done to identify adverse events and

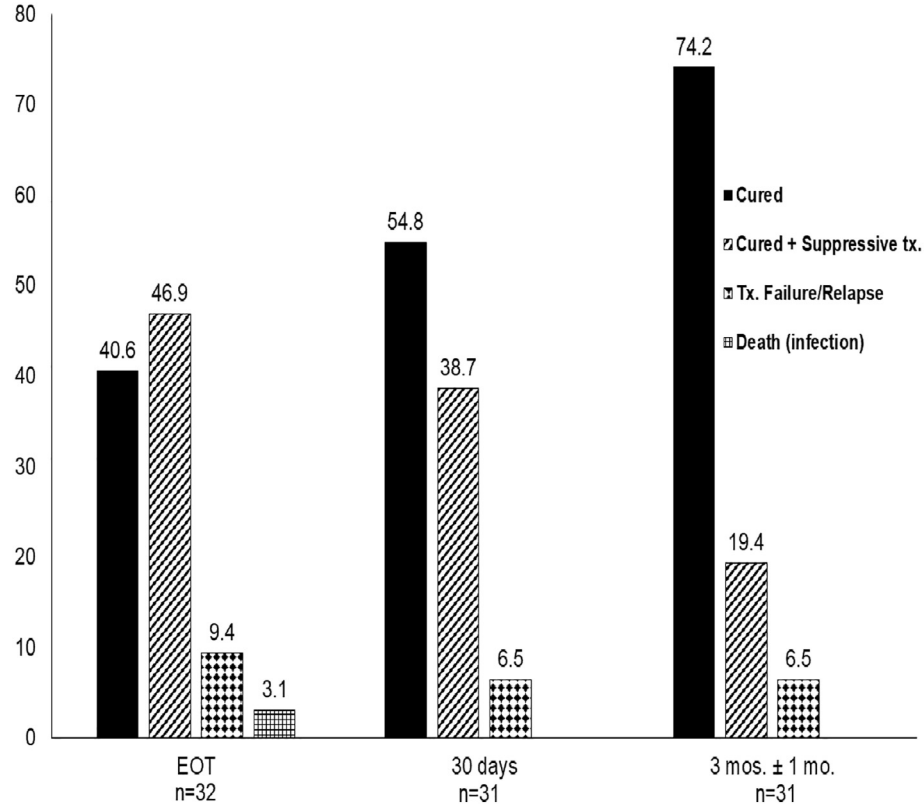

Fig. 1. Outcome of treatment for osteomyelitis at end of treatment (EOT), 30 days and 3 months after stopping telavancin.

has been used in similar observational studies looking at follow-up for osteomyelitis and evaluation of the specific agent (Lamp et al., 2007). Third, *S. aureus* isolates were not always collected to evaluate drug susceptibility to telavancin. Thus, since we had no isolates available for testing patients considered treatment failures, conclusions about drug failure and emergence of resistance cannot be drawn. Fourth, the indications or duration for the use of telavancin was left at the discretion of the treating clinician, a bias preventing any comparison to other trials. Finally, limitations of the study may also include possible confounding biases due to unmeasured variables.

Gram-positive infections are still the leading cause of osteomyelitis. With encountering an increased number of patients with reduced susceptibility to vancomycin, and daptomycin non-susceptible strains, additional treatment options are needed for the clinicians' consideration. The present study provides insight on how telavancin has been used to date by clinicians to treat osteomyelitis. There have been no randomized, controlled trials of telavancin for osteomyelitis and this study provides justification for performing such studies. The conduct of such trials may be very challenging because of the need for longer term follow-up to define successful therapy. Currently, vancomycin is still considered the treatment of choice for methicillin-resistant *S. aureus* osteomyelitis. ~~H~~However, limitations with the use of vancomycin do occur and justify the need for other drugs to be considered when vancomycin is not appropriate Although we cannot define the precise role of telavancin alone through this case series, we have provided descriptive information on how the drug is used in clinical practice as well as the outcome and tolerability for the use of telavancin in the treatment of osteomyelitis.

3.1. Conclusions

This study is not able to determine the efficacy of telavancin on osteomyelitis due to prior, post or concurrent use of other antimicrobial agents.

However, televancin was used as part of the antimicrobial regimen in many patients with osteomyelitis and demonstrated a favorable clinical outcome.

Declaration of Competing Interest

LDS, AH, JR and KC have participated in the speakers' bureau for Theravance. There were no other conflicts of interest for any of the other authors.

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