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Retrospective Comparison of Intravenous Therapy, Oral Therapy, and Lipoglycopeptides for the Treatment of Osteomyelitis

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Abstract: The use of Oral (PO) antibiotics and Lipoglycopeptides (LGP) is challenging the previous standard of Osteomyelitis (OM) treatment. This retrospective study included patients diagnosed with OM treated with Intravenous (IV) antibiotics, PO antibiotics, or LGP. The primary outcome was the occurrence of clinical failure within six months of therapy completion. Previous OM, surgical intervention as a part of management, presence of *Staphylococcus aureus* on culture, and other variables were included in a bivariate analysis, and variables with a p-value<0.2 were included in a multivariate regression. 257 patients received IV therapy, while the PO and LGP groups included 20 and 15 patients respectively. In the IV group, 89 (35%) of the patients experienced clinical treatment failure compared to 5 (25%) in the PO group and 5 (33%) in the lipoglycopeptide group (p = 0 .71). Median LOS was significantly shorter in the PO group compared to the IV and LGP groups [1 day (IQR 0-2.5) vs. 7 days (IQR 4-10) and 4 days (IQR 4-9), p = .003]. Only previous OM was included in the multivariate regression model [OR 1.75, 95% CI (1.07-2.87)]. Clinical outcomes were similar between the 3 groups. Previous OM at the index site being independently associated with treatment failure suggests that appropriate surgical intervention and antibiotic selection are of the utmost importance when managing OM. When feasible and appropriate, PO antibiotics and LGPs should be considered viable treatment options for OM.

Keywords: Osteomyelitis, Lipoglycopeptides, OPAT, Oral Therapy

Introduction

Intravenous (IV) antibiotics have long been the cornerstone of therapy for Osteomyelitis (OM). However, this treatment can be limiting for patients, as it often requires long-term catheter placement and some may not be candidates to administer IV therapy to themselves at home. Patients who are not candidates for IV therapy at home could then require prolonged stays within the healthcare system to complete an adequate course of treatment (Barshes *et al*., 2016; Tice *et al*., 2003; Spellberg and Lipsky, 2012; Cortés-Penfield and Kulkarni, 2019). Emerging evidence has demonstrated the safety and efficacy of Oral (PO) therapy for OM treatment, which would eliminate the need for patients to administer IV antibiotics at home or for long-term hospitalization (Li *et al*., 2019). Lipoglycopeptides (LGP), while lacking comparatively in terms of the breadth and quality of data found with PO therapy, are an intriguing treatment alternative for OM. These agents, dalbavancin and oritavancin, have long half-lives and excellent bone penetration, which can allow for single or multiple-dose infusions to be administered in clinic or at infusion centers (perhaps weekly), obfuscating the need for daily IV administration at home (Rappu *et al*., 2019; Chastain and Davis, 2019; Scoble and Tillotson, 2020; Dunne *et al*., 2015; Cain *et al*., 2022).

The VA St. Louis Health Care System provides a variety of options for OM treatment, including Outpatient Parenteral Antimicrobial Therapy (OPAT) or outpatient infusion of LGP, in addition to PO treatment for select patients. Some patients are also eligible for an

inpatient stay at a Community Living Center (CLC) for the duration of their IV antibiotic course. The objective of this study was to evaluate if IV antibiotics, PO antibiotics, and LGPs for the treatment of OM are associated with similar outcomes.

Materials and Methods

This retrospective, observational cohort study involved patients at the VA St. Louis Health Care System treated for OM with either IV, PO, or LGP therapy between January 1st, 2010, and June 1st, 2020. Patients in the IV treatment cohort were initially identified through clinical pharmacy records. At the St. Louis VA, clinical pharmacy specialists have managed all OPAT patients since 2008 and maintain a list of all VA St. Louis patients discharged on OPAT therapy; this list was used to identify cohort patients. Patients in the PO treatment group were initially identified by searching outpatient pharmacy dispensing records for anyone with a PO antibiotic prescription with a supply of ≥28 days and an ICD10 code (M86.0-86.9) for OM active at the time of prescribing. The LGP cohort was identified by searching inpatient and outpatient pharmacy dispensing records for any patient receiving LGP therapy for OM (determination of OM diagnosis discussed below in inclusion criteria).

To be included in the study patients had to have been between 18 and 89 years old at the time of treatment initiation and been treated for a case of OM. In addition to ICD10 criteria, all patients must have had confirmation of OM on bone pathology, or findings on imaging studies (e.g., Magnetic Resonance Imaging (MRI), Computerized Tomography (CT), or X-ray) consistent with OM as described by the reviewing radiologist, or a diagnosis of OM specifically stated in a note written by an infectious diseases physician. Within the IV therapy group patients were excluded from evaluation if they were given concomitant PO therapy or if they were given more than 1 week of PO therapy immediately following a course of IV treatment. Patients in the PO group could not have received >2 weeks of IV antibiotics prior to initiation of the PO course. Finally, patients in the LGP cohort must have received a minimum of 2 doses of dalbavancin or oritavancin to be eligible for inclusion.

The primary outcome was clinical treatment failure, which was defined as the need to re-initiate antibiotics or undergo unplanned surgical intervention for infection of the same anatomical site of the index case of OM within 6 months after treatment completion. Secondary outcomes included in-hospital Length Of Stay (LOS), amputation within 6 months of therapy completion, and occurrence of line-related or drug-related adverse events. Line-related adverse events were defined as line occlusion necessitating intervention, phlebitis, deep vein thrombosis, or line-related infection (documented within the medical record). Drug-related adverse events included *Clostridioides difficile* infection (defined by positive Polymerase Chain Reaction (PCR) test and positive toxin immunoassay and documented watery stools four or more times daily in the medical record), acute kidney injury (defined as a rise in creatinine of at least 0.3 mg/dL or 1.5 times baseline, or urine output of <0.5 mL/kg/hr over 6-12 h), or nausea, vomiting, diarrhea, headache, or rash (documented within the medical record and thought to be related to study medication).

Descriptive statistics were used to compare baseline characteristics between the three groups. Categorical variables across groups were compared using chi-square and Fisher's exact test as appropriate, while LOS was analyzed using Mood's median test. A two-sided alpha value of .05 was used to determine significance. A bivariate analysis was conducted on the following variables to determine if they were associated with treatment failure: Previous OM at index site, surgical intervention as a part of initial management, presence of *Staphylococcus aureus* on culture, utilization of OPAT services (IV group only) and concomitant PO therapy (LGP group only). Variables with a p-value <.2 were included in a multivariate regression model. Statistical analyses were completed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). This study was approved by the Institutional Review Board at the VA St. Louis health care system.

Results

292 patients were included in the study: 257 in the IV group, 20 in the PO group, and 15 in the LGP group. Baseline characteristics are shown in Table (1). No significant differences were found between groups, although the imaging method and type of culture collection were not statistically analyzed. Previous OM at the index site of infection was common, with 35.8, 50.0, and 46.7% in the IV, PO, and LGP groups respectively. An MRI was collected in 57.2 and 60% of the IV and LGP patients respectively, compared to only 25% in the PO group. 35% of the patients in the PO group had no imaging, compared to only 3.9% in the IV group (all patients in the LGP group had imaging). Pathology collection followed a similar trend with lower occurrence in the PO group compared to the other two, albeit not statistically significant (Table 1). Antibiotic selections for the IV, PO, and LGP groups are shown in Tables (2-3).

The primary outcome of clinical treatment failure occurred in 34.6% (89/257) of the IV patients, 25% (5/20) of the PO patients and 33.3% (5/15) of the LGP patients (P = .71). Median LOS was 7 days (IQR 4-10) in the IV group, 1 day (IQR 0-2.5) in the PO group and 4 days (IQR 4-9) in the LGP group (P = .003). The secondary outcomes of amputation within 6 months and incidence of drug-related adverse events were not significantly different between the three groups (Table 4).

Table 1: Baseline characteristics

Characteristic	IV Group (n = 257)	PO Group (n = 20)	LGP Group (n = 15)	p-value
Age, years (mean ± SD)	64.9 ± 8.7	64.3 ± 9.1	64.3 ± 9.3	0.93
Gender – male, n (%)	250 (97.3)	20 (100)	15 (100)	1
Race, n (%)				---
White	201 (78.2)	14 (70.0)	11 (73.3)	
African Am.	52 (20.2)	6 (30.0)	4 (26.7)	
Other	4 (1.6)	0 (0)	0 (0)	
Diabetes, n (%)	207 (80.5)	14 (70.0)	14 (93.3)	0.25
Peripheral Vascular Disease, n (%)	88 (34.2)	4 (20.0)	4 (26.7)	0.4
Creatinine Clearance <30 mL/min, n (%)	13 (5.1)	2 (10.0)	0 (0)	0.41
Previous OM at Index Site, n (%)	92 (35.8)	10 (50.0)	7 (46.7)	0.33
Imaging, n (%)				---
None	10 (3.9)	7 (35.0)	0 (0)	
X-ray	87 (33.9)	6 (30.0)	5 (33.3)	
CT	13 (5.1)	2 (10.0)	1 (6.7)	
MRI	147 (57.2)	5 (25.0)	9 (60.0)	
Culture collected, n (%)				---
No Culture				
Swab	34 (13.2)	5 (25.0)	4 (26.7)	
Tissue	124 (48.3)	8 (40.0)	1 (6.7)	
Bone	32 (12.5)	1 (5.0)	2 (13.3)	
	65 (25.3)	6 (30.0)	8 (53.3)	
Pathology Collected, n (%)	125 (48.6)	5 (20.0)	7 (46.7)	0.13
Surgical treatment, n (%)	149 (58.0)	8 (40.0)	6 (40.0)	0.13
Amputation, n (%)	81 (31.5)	4 (20.0)	8 (53.3)	0.11
S. aureus on Culture, n (%)	88 (34.2)	4 (20.0)	2 (20.0)	>0.05
P. aeruginosa on Culture, n (%)	21 (8.2)	1 (5.0)	1 (6.7)	>0.05

Table 2: Antibiotic selection for patients receiving IV antibiotics

Patients in the IV therapy group receiving monotherapy (N = 119)	
Agent	n (%)
Ceftriaxone	42 (35.2)
Ertapenem	16 (13.4)
Piperacillin-tazobactam	14 (11.8)
Vancomycin	13 (10.9)
Ceftaroline	8 (6.7)
Daptomycin	8 (6.7)
Cefepime	7 (5.9)
Cefazolin	3 (2.5)
Meropenem	3 (2.5)
Ampicillin-sulbactam	2 (1.7)
Penicillin G	1 (0.840
Nafcillin	1 (0.84)
Patients in the IV therapy group receiving combination therapy with 2 agents (N = 112)	
Cefepime (n = 32)	
Vancomycin + cefepime	27 (24.1)
Daptomycin + cefepime	5 (4.5)
Ertapenem (n = 23)	
Vancomycin + ertapenem	17 (15.2)
Daptomycin + ertapenem	6 (5.4)
Ceftriaxone (n = 21)	
Vancomycin + ceftriaxone	15 (13.4)
Daptomycin + ceftriaxone	6 (5.4)
Metronidazole (n = 13)	
Metronidazole + ceftriaxone	6 (5.4)
Metronidazole + cefepime	4 (3.6)
Metronidazole + ceftaroline	3 (2.7)
Meropenem (n = 10)	
Daptomycin + meropenem	8 (7.1)
Vancomycin + meropenem	2 (1.8)
Piperacillin-tazobactam (n = 9)	
Vancomycin + pip-tazo	7 (6.2)
Daptomycin + pip-tazo	2 (1.8)
Levofloxacin + daptomycin	1 (0.9)
Patients in the IV therapy group receiving combination therapy with 3 agents (N = 26)	

Table 3: Antibiotic selection for patients receiving PO and LGP antibiotics

PO antibiotic (n = 20)	n (%)
Fluoroquinolone	12 (60.0)
Beta-lactam	4 (20.0)
Clindamycin	4 (20.0)
Sulfamethoxazole-trimethoprim	3 (15.0)
Linezolid	3 (15.0)
Doxycycline	1 (5.0)
Combination	8 (40.0)
LGP antibiotic (n = 15)	n (%)
Dalbavancin	13 (86.7)
Oritavancin	2 (13.3)
Concomitant PO antibiotics	11 (73.3)

Table 4: Primary and secondary outcomes

Outcome	IV group (n = 257)	PO group (n = 20)	LGP group (n = 15)	P-value
Treatment failure, n (%)	89 (34.6)	5 (25)	5 (33.3)	0.71
Amputation within 6 months of treatment completion, n (%)	27 (10.5)	0	3 (20)	0.12
Adverse events (drug-related)[1], n (%)	50 (19.5)	4 (20)	0	0.16
Acute kidney Injury, n (%)	27 (10.5)	3 (15)	3 (20)	0.46
Line-related adverse events[2], n (%)	17 (6.6)	---	---	---
CDAD[3], n (%)	7 (2.7)	0	0	>0.05

[1]Adverse events (drug-related): Any nausea, vomiting, diarrhea (CDAD or non-CDAD), headache, or rash documented in the medical record and believed by the provider to be related to the antimicrobial regimen; [2]Line-related adverse events: Phlebitis, thrombosis, or line-related infection documented in the medical record; [3]Clostridioides difficile-associated diarrhea

Table 5: Bivariate analysis

Variable	p-value
Primary PO therapy	0.47
Primary LGP therapy	1.00
Previous OM at index site	0.03
Surgical treatment performed	0.94
Staphylococcus aureus on culture	0.84
OPAT used (IV group only)	0.56
Concomitant PO therapy (LGP group only)	1.00

Among the variables included in the bivariate analysis, only previous OM at the index site met the criteria for inclusion in the multivariate analysis (Table 5). In the multivariate regression model, previous OM at the index site was independently associated with treatment failure at 6 months (odds ratio [OR], 1.75; 95% CI, 1.07–2.87).

Discussion

In this three-armed retrospective cohort study, no difference in clinical treatment failure rates was observed between IV therapy, PO therapy, and LGP therapy for OM. This finding adds to the available evidence supporting the use of PO antibiotics and LGPs in the management of this infection.

LOS was found to be significantly shorter in the PO group compared to the IV and LGP arms. This was expected, as patients often considered for PO therapy are stable enough for an outpatient setting, likely not good candidates for IV therapy, and may need or want to get out of the hospital sooner. The higher number of patients who had no imaging obtained, no amputations, and no pathology collected in the PO group is also congruent with this. Less frequent administration and the ability to quickly discharge from the hospital are often touted as advantages of LGPs but shortened LOS as a result of LGP use was not observed in this study. A contributing factor to this may be that dalbavancin and oritavancin are still not thought of as first-line options, but rather novel agents that are considered later into treatment courses once patients are pending discharge, or they are determined to not be candidates for OPAT.

Antibiotic selection in the IV group (Table 2) varied widely, with 119 patients having received monotherapy, 112 combination therapy with two agents, and 26 with three agents. This variation was to be expected based on the variety of organisms found in osteomyelitis cases as well as the common need for empiric treatment in the setting of a lack of quality culture collection. Ceftriaxone monotherapy was the most common regimen overall in this group, followed by vancomycin plus cefepime and vancomycin plus ertapenem. In terms of antibiotics selected for the PO group, fluoroquinolones were the most prescribed antimicrobials. As a class, fluoroquinolones have high oral bioavailability, are known to penetrate bone sufficiently, and provide a broad spectrum of antimicrobial coverage, likely lending to their preferential use. Fluoroquinolones are associated with some untoward side effects, particularly when used for long periods of time, but adverse event rates were comparable between the IV and PO groups in this study, suggesting there is still a population where this modality can and should be considered. Dalbavancin was given to most patients in the LGP group, each receiving a 2-dose series given one week apart; only one patient who received oritavancin received 3 doses for treatment. This distribution is not surprising as there has been a preference at the VA St. Louis to use dalbavancin over oritavancin for OM, in part due to the more robust pharmacokinetic modeling to support a specific dosing regimen (Dunne *et al.*, 2015).

The bivariate and multivariate analysis conducted in this study found that previous osteomyelitis at the index site was the only factor tested that was associated independently with treatment failure. Although this is consistent with previous knowledge, it is interesting that other factors found in previous studies to be associated with treatment failure were not found to be significant here. For example, one study identified that the absence of surgical intervention along with the duration of osteomyelitis greater than 3 months and bone exposure were predictors of treatment failure (Garcia del Pozo *et al.*, 2018). It has also been described in the literature that infections with *Staphylococcus aureus* can lend themselves to higher rates of recurrence due to its ability to form biofilms (Kavanagh *et al.*, 2018). In this study, however, neither the absence of surgical intervention nor infection with *Staphylococcus aureus* was independently associated with treatment failure.

In comparing the present results to those observed by Li *et al.* (2019) in the OVIVA trial we find that a total of 14% (141/1015) of patients randomized experienced definitive treatment failure 14.6% (74/506) in the IV group and 13.2% (67/509) in the PO group. The overall treatment failure rate in this study was substantially higher than that in the OVIVA trial (34% (99/292) vs 14% (141/1015)), but it is important to keep in mind that the definition of failure was different in OVIVA, 1 clinical criterion (draining sinus tract from bone or prosthesis or frank pus adjacent to bone or prosthesis, or presence of a microbiologic criterion, or presence of a pathologic criterion) must have been observed in the 12 months after randomization to be defined as having failed therapy. Additionally, two important points to consider that could have contributed to the difference in outcomes between studies is that the present evaluation contains a higher percentage of patients with important comorbidities (diabetes: 80.5% (235/292) vs. 19.5% (205/1054) in OVIVA; peripheral vascular disease: 32.9% (96/292) vs. 6% (63/1054) in OVIVA) which can make treatment success more difficult to achieve. Finally, 76.7% (805/1049) of patients in the OVIVA trial had therapy

continued beyond the planned 6 weeks; the median total duration of therapy was 78 days in the PO group and 71 days in the IV group (Li *et al.*, 2019). In the present study, the need to continue antibiotics beyond the originally planned stop-date could have been considered a criterion for treatment failure.

Fewer well-designed, prospective trials evaluating the benefits of LGPs in the management of OM are available. One example by Rappo *et al*. (2019) evaluated 2 doses of 1500mg of dalbavancin given 1 week apart to the Standard-Of-Care (SOC) for the treatment of OM. Clinical cure was demonstrated in 97% (65/67) in the dalbavancin group and 88% (7/8) in the SOC group. This evaluation reflects the same dosing scheme that was used by Rappo *et al*. (2019) (this is the preferred dosing for OM at the VA St. Louis), but major differences between the evaluations include, again, a population with a significantly higher prevalence of diabetes and vascular disease and the definition and timing of the primary outcome (Rappo *et al*. (2019) evaluated treatment failure at completion of therapy for the primary outcome). A very recent retrospective, observational cohort study by Cain *et al*. (2022) evaluated this 2-dose dalbavancin regimen compared to SOC in OM patients at 2 hospitals in Pennsylvania. The failure rate found by Cain *et al*. (2022) was closer to what was observed in the present study (21.4% (9/42) treated with dalbavancin and 23.3% (21/90) treated with SOC). Patients in the Cain *et al*. (2022) study treated with dalbavancin did have a shorter hospital LOS, which was not observed in this trial. The Cain *et al*. (2022) study population does more closely mimic the present population in regard to patients with diabetes (46.2% (61/132)), but not in patients with peripheral vascular disease (3.8% (5/132)) (Cain *et al.*, 2022).

The unique design of this study is its foremost strength. The authors of this study were unable to find any published studies comparing these 3 treatment modalities to one another. The authors believe this better reflects clinical practice, as treatment decisions are not often made between two options alone. Second, the study population is representative of a veteran population with common risk factors for OM, including diabetes and peripheral vascular disease; something not present in other trials evaluating similar treatment options. Within the VA system, these results carry a high level of external validity. Third, this study included OM cases with a wide range of bacterial pathogens, including 32.5% methicillin-resistant *Staphylococcus aureus* cases and 7.9% *Pseudomonas aeruginosa* cases. The distribution is similar to the OVIVA trial, which had 37.7% *S. aureus* cases and 5.1% *P. aeruginosa* cases. The present study differs significantly in the number of polymicrobial cases in 44.9% of the current population compared to 14.5% in OVIVA (Li *et al.*, 2019). Thus, these results are applicable to a range of bacterial causes of OM in very complex patients.

This study is not without limitations. First, the groups were not matched, introducing the possibility of selection bias. Future retrospective reviews of this nature could employ propensity score matching to increase the strength of findings. Second, while this study utilized a robust data set for the IV patients, both the PO and LGP groups did not meet power. For the LGP group, the small population is reflective of their infrequency of use in the treatment of OM; LGP groups in other studies have faced a similar issue. For example, the two largest trials supporting the use of oritavancin and dalbavancin for the treatment of OM contain only 23 and 70 patients in their lipoglycopeptide groups respectively (Rappo *et al*., 2019; Scoble and Tillotson, 2020). The small sample size in the PO group was due in part to the difficulties encountered with appropriately identifying potential patients for inclusion. Lastly, clinical failure rates across the study population were underestimated in our power calculation. For future studies, a higher expected failure rate should be used to estimate appropriate sample sizes.

Conclusion

In conclusion, this study supports the use of PO antibiotics and LGPs as alternative options to IV antibiotics for the treatment of OM. The only factor independently associated with clinical failure was previous osteomyelitis at the index site, suggesting that the best chance for treatment success is with the first course. This highlights the importance of appropriate surgical treatment and antibiotic selection in the management of OM. Further research substantiating the use of OM treatment alternatives will be paramount in optimizing patient outcomes in the future.

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Author's Contributions

Alexander Joseph Stumphauzer: Concept and design; data procurement; statistical testing; analysis and interpretation; writing and editing of ongoing drafts.

Ryan Paul Moenster: Concept and design; analysis and interpretation; editing of ongoing manuscript drafts.

Travis Linneman: Concept and design, review of early manuscript drafts.

Ethics

This study was approved by the institutional review board at the VA St. louis health care system.

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