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Long-Acting Lipoglycopeptides for the Treatment of Bone and Joint Infections and Bacteremia in Infectious Disease Outpatient Infusion Clinics

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Abstract

Background: Long-acting lipoglycopeptides (LGPs) are approved for the treatment of acute bacterial skin and skin-structure infections. Broad Gram-positive coverage and weekly dosing regimens are useful for other diagnoses, but real-world data supporting such use are sparse. We review our experience of dalbavancin and oritavancin for the treatment of bone and joint infection (BJI) and bacteremia (BAC) in outpatient infusion clinics (OICs).

Methods: We conducted a multicenter, retrospective, observational cohort study of patients (pts) receiving long-acting LGPs in OICs over 2 yrs from 2018-2019 for BJI and BAC. Data collected included demographics, diagnosis, dosing regimen, microbiology, clinical outcomes, and adverse events (AEs). Clinical success, defined as resolution of infection with continued oral antibiotics allowed, was assessed at the next follow-up visit. Worsening infection, the need for additional intravenous therapy, and discontinuations during therapy were deemed non-successful.

Results: We identified 70 pts (mean age: 64±16 years, 53% male) from 25 OICs, who received dalbavancin (n=50), oritavancin (n=19) and both (n=1). BJI accounted for 55 (79%) with 31 osteomyelitis, 9 bursitis, 7 prosthetic joint, 7 septic arthritis and 1 tenosynovitis. BAC was the primary diagnosis in 15 (21%) and sources were 6 device, 2 lower respiratory tract, 2 urinary tract and 5 unknown. 46% of pts were treated in the OIC without prior hospitalization. 72 Gram-positive isolates were obtained from 67 pts, with *Staphylococcus aureus* predominant (42/72, 58%), including methicillin-resistant (26/72, 36%) and methicillin-susceptible isolates (16/72, 22%). Median number of doses administered were 2 [IQR 1-2] in BJI and 1 in BAC [IQR 1-2]. Overall clinical success was 86% (57/66), with 4 non-evaluable. BJI had 85% success (44/52), with 90% in osteomyelitis (28/31), 50% in prosthetic joint (3/6) and 87% (13/15) in the others. Clinical success was 93% (13/14) in BAC. Three pts (4%) on dalbavancin experienced mild AEs, none resulting in discontinuation of therapy.

Conclusions: This multicenter real-world study of long-acting LGPs demonstrates safety and high clinical success rates in BJI and BAC. Our experience suggests a role for use of these agents in the treatment of BJI and BAC in the outpatient setting.

Objectives

The indications for the clinical use of LPG with single intravenous infusions have seen increasing use in many care settings and for diagnoses other than complicated bacterial skin and skin structure infections [1, 2].

The objective of our study was to report our experience of the use of dalbavancin and oritavancin for treatment of bone and joint infections (BJI) and bacteremia (BAC) in the outpatient setting.

Methods

Study design: Multicenter, retrospective cohort study

Location: U.S. physician office infusion center (n=25)

Study population: Patients (pts) treated intravenously (IV) with dalbavancin and/or oritavancin during 2018 and 2019 for BJI and BAC

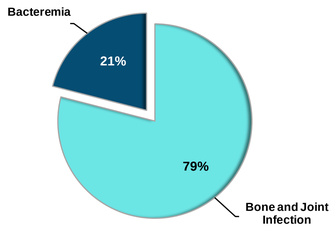
Data collection: Demographics, prior therapy and location, comorbidities, microbiology, dosing regimens, clinical outcomes at follow-up assessment, and reported adverse events (AE)

Outcome: Clinical success was defined as resolution of infection with continued oral antibiotics allowed. The need for continued IV antibiotic therapy or premature discontinuation of long-acting LGPs due to lack of efficacy or AE were recorded as non-success.

Statistical analysis: Descriptive statistics were applied using mean and standard deviation (SD) or medians (range) and for categorical variables numbers and percentages. Results were stratified by diagnosis. Bivariate analysis of clinical outcome was performed using *t*-test for continuous and Chi-square for categorical variables with $P < 0.05$ defined as statistically significant.

Study Cohort

- 70 pts from 25 OICs received long-acting LGPs for BJI and BAC
- BJI (n=55) included 31 osteomyelitis, 9 bursitis, 7 prosthetic joint infections, 7 septic arthritis, and 1 tenosynovitis
- BAC (n=15) included 6 device infections as well as bacteremia originated from 2 pyelonephritis, 2 lower respiratory tract infections, and 5 of unknown sources



Demographics and Clinical Characteristics

Variable	BJI	BAC	Total
No. of patients (%)	**55 (79)**	**15 (21)**	**70 (100)**
Age in years			
mean±SD	65±15	62±19	64±16
≥65	31 (56)	8 (53)	39 (56)
Sex, male	30 (54)	7 (47)	37 (53)
Prior hospitalization	27 (49)	11 (73)	38 (54)
inpatient days, median (range)	5 (2-20)	5 (4-18)	5 (2-20)
Prior IVAB[1] therapy	28 (51)	13 (87)	41 (59)
length of prior IVAB, median (range)	11 (2-30)	5 (3-27)	8 (2-30)
Charlson index, mean±SD	4.9±2.2	6.1±3.0	5.1±2.4
Significant comorbidities			
cardiovascular disease	44 (80)	11 (73)	55 (79)
rheumatoid arthritis/osteoarthritis	25 (45)	7 (47)	32 (46)
diabetes mellitus	19 (34)	3 (20)	22 (31)
obesity[2]	17 (31)	4 (27)	21 (30)
malignancy	10 (18)	6 (40)	16 (23)
substance abuse	5 (9)	-	5 (7)
Type of long-acting lipoglycopeptide			
dalbavancin	38 (69)	12 (80)	50 (71)
oritavancin	16 (29)	3 (20)	19 (27)
dalbavancin/oritavancin	1 (2)	-	1 (2)

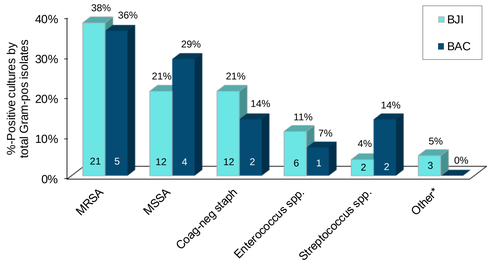
[1]; Intravenous antibiotic (IVAB) therapy within 7 days prior to start of LGP therapy. Prior IVAB included vancomycin in 26, cephalosporins in 8, daptomycin in 5, and 2 unknown

[2]; defined as body mass index ≥30 kg/m^2.

Results

Microbiology

- 72 Gram-positive pathogens were isolated from 67 patients



*; Others included *Peptostreptococcus magnus* (n=2) and *Gardnerella vaginalis* (n=1).

- In the BJI group, 8 pts reported 2 Gram-positive pathogens and 3 had mixed Gram-positive & Gram-negative infections

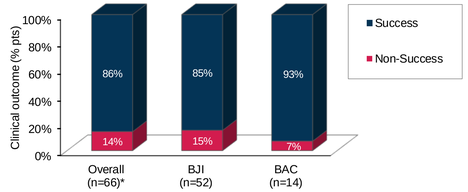
Dosing Regimen by Diagnosis

Dose Regimen of Long-acting Lipoglycopeptides (Dose Range / Frequency)		No. of Patients BJI	BAC
Dalbavancin		**38**	**12**
Single dose	1000 mg to 1500 mg d1	18	7
Multiple doses	*2-dose regimen**		
	500 to 1500 mg d1, d8	12	4
	3-dose regimen		
	500 to 1000 mg d1, d8, d15	2	1
	*6-dose regimen***		
	500 to 1500 mg weekly	4	-
	*>6-dose regimen***		
	500 to 1000 mg weekly	2	-
Oritavancin		**16**	**3**
Single dose	1200 mg d1	9	2
Multiple doses	*2 -dose regimen*		
	1200 mg d1, d15	3	-
	3-dose regimen		
	1200 mg d1, d15, d29	1	-
	4-dose regimen		
	1200 mg d1, d15, d29, d43	1	-
	≥5-dose regimen		
	1200 mg weekly	2	1

*; One pt received 1500 mg d1 dalbavancin followed by 1200 mg d15 oritavancin.

**; initial dose higher than following doses.

Clinical Outcome by Diagnosis



- Overall clinical success was 86% (n=57) including 41% requiring continued oral antibiotics. Median time from end of LGP therapy to next follow-up visit was 15 days (range, 1 to 81).
- Success rate for BJI was 85% (44 of 52), with 21 (40%) receiving prior IVAB
- Success rate for BAC was 93% (13 of 14), with 12 (86%) receiving prior IVAB
- Non-success was reported for 8 BJI and 1 BAC pts due to worsening or recurrent infection. Two pts had new organisms identified.
- Outcomes were unavailable for 4 pts
- 5 AEs were reported in 3 dalbavancin pts (2 fatigue, 2 nausea, 1 vomiting). No discontinuations of planned infusions were noted due to AEs.

Clinical Outcome Specified by Sub-Diagnoses

Diagnosis	N	Clinical Outcome Success (n, %)	Non-Success (n, %)
BJI	**52**	**44 (85%)**	**8 (15%)**
Osteomyelitis	31	28 (90%)	3 (10%)
Bursitis	7	7 (100%)	-
Prosthetic joint infection	6	3 (50%)	3 (50%)
Septic arthritis	7	5 (71%)	2 (29%)
Tenosynovitis	1	1 (100%)	-
BAC	**14**	**13 (93%)**	**1 (7%)**
Device infection	5	4 (80%)	1 (20%)
Pyelonephritis	2	2 (100%)	-
Lower respiratory tract infection	2	2 (100%)	-
Unknown source	5	5 (100%)	-

Bivariate Analysis of Clinical Outcome

Baseline Variable	Clinical Success Yes (n=57)	No (n=9)	*P*-value*
Age, mean±SD	**62±16**	**76±11**	**0.014**
Female, n (%)	27 (47%)	5 (56%)	0.648
Charlson index, mean±SD	5.0±2.4	5.7±1.9	0.408
Diagnosis, BJI	44 (77%)	8 (89%)	0.425
Missed dose during LGP therapy	5 (9%)	2 (22%)	0.223

Discussion

A multicenter retrospective study was performed of patients receiving long-acting LGPs in Infectious Disease physician office infusion clinics for BJI and BAC in 2018 and 2019.

- 70 pts received dalbavancin or oritavancin in 25 OICs.
- 46% of pts were treated entirely in the outpatient setting, having not been previously hospitalized. The remainder received LGP in the outpatient setting following a hospital discharge.
- Nearly 60% received other IV antibiotics prior to LPG therapy, but all received their first dose of LPG in the OIC.
- Most frequent Gram-positive pathogens were MRSA (36%), MSSA (22%), and coagulase-negative staphylococci (20%).
- The median number of doses administered for BJI was 2 (range: 1 to 12) and for BAC was 1 (range: 1 to 5).
- Overall clinical success rate of long-acting LGPs was 93% for BAC and 85% for BJI.
- Advanced age was a significant risk factor for poor outcome.
- Dalbavancin and oritavancin were well tolerated.
- Data on the clinical outcome of LGPs for BAC and BJI are limited. Randomized clinical trials in BJI have been published in pediatrics and more recently in adults using a 2-dose regimen of dalbavancin.[4,5] Guidance for clinicians to use LGPs in the treatment of adults with BJI and BAC has been sparse, and trial data were not published until 2019.[3]
- Limitations are related to the retrospective nature of this study and variations in dosing without a control group. Follow-up data varied based on patient visits and reports. Adverse events were limited only to reports received after treatment and may not be inclusive.

Conclusions

- ❑ **This multicenter real-world study of long-acting LGPs demonstrated successful clinical outcomes in BJI and BAC.**
- ❑ **Dalbavancin and oritavancin were reported to be safe even with multiple infusions.**
- ❑ **Our experience suggests that long-acting LGPs may be beneficial for the treatment of BJI or BAC in the outpatient setting, but more data regarding optimal dosing are needed.**

References

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