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Clinical Experience with Telavancin for the Treatment of Patients with Bone and Joint Infections: Preliminary Results from the Telavancin Observational Use Registry (TOUR™)

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INTRODUCTION AND PURPOSE

- Bone and joint infections, commonly caused by Gram-positive pathogens, including *Staphylococcus aureus*, often require prolonged antimicrobial therapy[1,2]
- Telavancin (TLV) is a lipoglycopeptide antibacterial active against susceptible Gram-positive pathogens, including methicillin-sensitive and -resistant *Staphylococcus aureus* (MSSA and MRSA) that is administered intravenously once daily, and is suitable for both inpatient and outpatient use[3-5]
- In the US, TLV is approved in adults for the treatment of complicated skin and skin-structure infections (cSSSI) and hospital-acquired bacterial and ventilator-associated bacterial pneumonia (HABP/VABP) when alternative treatments are not suitable[5]
- In Canada and Russia, TLV is approved for cSSSI and HABP/VABP, while in the European Union, TLV is approved for the treatment of nosocomial pneumonia, known or believed to be caused by MRSA when other alternative medicines are unsuitable[6,7]
- Telavancin provided comparable efficacy to vancomycin in a limited number of patients with either cSSSI or HABP/VABP and concurrent *S. aureus* bacteremia[5]
- The Telavancin Observational Use Registry (TOUR™) is a multicenter registry designed to characterize real-world TLV usage patterns to assess population characteristics and clinical outcomes associated with its use for Gram-positive infections[8]
- Here we present the characteristics, TLV dosing patterns, and clinical outcomes for a subset of TOUR™ patients with bone and joint infections

METHODS

TOUR™ Design and Methodology

- TOUR™ collected data from approximately 1155 patients from 46 US hospitals or outpatient infusion centers
- Any patient who received at least 1 dose of TLV after January 1, 2015, was eligible for inclusion (individuals who participated in any TLV clinical study were excluded)
- All treatment decisions and clinical assessments were at the discretion of the treating physician, and data were obtained via retrospective medical chart review

Data Collection and Analyses

- Data, including demographics, primary infection type, baseline pathogens, duration of hospitalization, prior or concomitant antimicrobial treatment, TLV dosing regimen, clinical response, adverse events (AEs) of interest, and 28-day mortality, were entered directly into electronic case report forms
- Adverse event data collection was limited to renal AEs and AEs leading to discontinuation or a fatal outcome
- Clinical outcome at end of therapy was designated as positive clinical response (cured or improved to step-down therapy), nonevaluable (indeterminate, missing, or undocumented), or failure
- Descriptive analyses were performed

RESULTS

- At the preliminary cutoff date of September 30, 2016, data had been collected from 36 sites for 593 patients, 174 (29%) of them with bone and joint infections **(Table 1)**
- Common comorbidities were hypertension (86 [49.4%]) and type 2 diabetes mellitus (71 [40.8%])
- The predominant baseline pathogen was MRSA **(Table 2)**
- The median TLV dose and duration of treatment were 8.7 mg/kg (interquartile range [IQR] 7.1, 10.0) and 26 days (IQR 14, 42 days), respectively **(Table 3)**
- Patients were dosed as per their baseline creatinine clearance **(Table 4)**
- Telavancin was used as a salvage therapy in 126 (72.4%) patients
- The majority of patients were treated as outpatients **(Table 5)**
- Positive clinical response at the end of TLV therapy was observed in 68.4% of patients, while 10.3% of patients failed treatment, and 21.3% were not evaluable **(Figure 1)**
- Of the 174 patients, (amendment 1–18, amendment 2–156), a total of 33 patients reported at least 1 AE of interest (**Table 6**), 7 experienced 1 or more serious AEs, 20 had an AE that led to drug discontinuation, and 3 died within 28 days of the first TLV dose

Table 1. Baseline Demographics and Clinical Characteristics

Characteristic	Frequency (N = 174)
Age (years)*	
Mean (SD)	57.2 (13.37)
Median (range)	58.0 (18–92)
Age distribution, n (%)	
<65 years	123 (71.5)
≥65 years	49 (28.5)
Sex, n (%)†	
Male	119 (68.8)
Female	54 (31.2)
Ethnicity, n (%)†	
Hispanic or Latino	3 (1.7)
Not Hispanic or Latino	163 (94.2)
Not Reported or Unknown	7 (4.0)
Race, n (%)	
American Indian or Alaskan Native	3 (1.7)
Asian	2 (1.2)
Black or African American	13 (7.5)
White	151 (87.3)
Other	4 (2.3)
Height (cm)‡	
Mean (SD)	176.3 (10.76)
Median (range)	177.8 (152.0–203.2)
Weight (kg)‡	
Mean (SD)	95.2 (24.73)
Median (range)	93.9 (44.5–196.4)
BMI (kg/m²)‡	
Mean (SD)	30.5 (6.83)
Median (range)	29.1 (18.1–61.5)

*Measurements not recorded for 2 patients
†Measurements not recorded for 1 patients
‡Measurements not recorded for 3 patients
BMI, body mass index; SD, standard deviation

Table 2. Gram-positive Baseline Pathogens

Pathogen*	Frequency (%)
Methicillin-resistant *Staphylococcus aureus*	70 (40.2)
Methicillin-sensitive *Staphylococcus aureus*	24 (13.8)
Coagulase-negative Staphylococcus	11 (6.3)
Enterococcus faecalis	5 (2.9)
Group B Streptococcus	6 (3.4)
Group A Streptococcus	1 (0.6)

*30 patients reported other pathogens. More than 1 pathogen was detected in 132 patients, with Gram-negative pathogens, including *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, isolated as a part of a mixed Gram-positive and Gram-negative infection. Baseline pathogen was not recorded in 42 patients

Table 3. Telavancin Dosing and Treatment Duration

Telavancin Exposure Characteristics	Patients (N = 174)
Average daily dose (mg)*	
Mean (SD)	785.2 (169.61)
Median (IQR)	750.0 (750.0, 750.0)
Average daily dose per bodyweight (mg/kg)†	
Mean (SD)	8.6 (2.08)
Median (IQR)	8.7 (7.1, 10.0)
Duration of TLV dosing (days)*	
Mean (SD)	29.2 (33.69)
Median (IQR)	26.0 (14, 42)
Dose adjusted, n (%)	
No	147 (84.5)
Yes	19 (10.9)
Missing	8 (4.6)

*8 and †10 patients, respectively
IQR, interquartile range; SD, standard deviation; TLV, telavancin

Table 4. Telavancin Dosing by Baseline Creatinine Clearance

Telavancin Exposure Characteristics	Baseline CrCL (mL/min)*			
	<30 (n = 1)	30–<50 (n = 1)	50–<80 (n = 21)	≥80 (n = 76)
Average daily dose (mg)				
Mean (SD)	743.6 (n/a)	700.0 (n/a)	744.1 (74.23)	818.2 (184.59)
Median (IQR)	743.6 (743.6, 743.6)	700.0 (700.0, 700.0)	750.0 (750.0, 750.0)	750.0 (500.0, 890.0)
Treatment duration (days)				
Mean (SD)	49.0 (n/a)	7.0 (n/a)	29.0 (19.98)	32.2 (46.52)
Median (IQR)	49.0 (49, 49)	7.0 (7, 7)	26.0 (14, 42)	25.0 (15, 42)
Average daily dose per bodyweight (mg/kg)				
Mean (SD)	11.5 (n/a)	8.4 (n/a)	9.3 (1.79)	8.4 (1.68)
Median (IQR)	11.5 (11.5, 11.5)	8.4 (8.4, 8.4)	8.9 (8.5, 10.1)	8.4 (7.1, 9.8)
Dose adjusted, n (%)				
No	0 (0)	1 (100)	16 (76.2)	69 (90.8)
Yes	1 (100)	0 (0)	5 (23.8)	7 (9.2)

*Baseline CrCL-based telavancin dosing was not estimated for 75 patients due to missing serum creatinine
CrCL, creatinine clearance; IQR, interquartile range; n/a, not applicable; SD, standard deviation

Table 5. Patient Care Setting at Telavancin Initiation

Care Setting	Frequency (%)
Inpatient	21 (12.1)
Hospital floor	20 (11.5)
Intensive care unit	1 (0.6)
Outpatient	107 (61.5)
Home	7 (4.0)
Clinic	52 (29.9)
Infusion center	48 (27.6)
Missing	46 (26.4)

Figure 1. Clinical Outcomes at End of Therapy (N = 174)

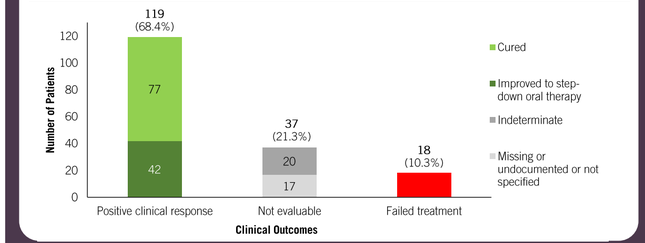

Table 6. Frequency of Reported Adverse Events of Interest (≥1%)

MedDRA Preferred Term	Frequency (%)
Infusion-related reaction	2 (1.1)
Nausea	4 (2.3)
Nephrotoxicity* (Nephropathy toxic)	7 (4.0)
Renal failure†	15 (8.6)

*Prior to amendment 2 of the TOUR protocol, adverse events of interest included nephrotoxicity, infusion reactions, QTc >500 msec, nausea or vomiting of moderate or severe intensity, and hypersensitivity reactions. These reports were under amendment 1, which required a report of a nephrotoxicity adverse event for any change in serum creatinine of ≥0.5 mg/dL or ≥50% regardless of clinical significance or relationship to normal reference range. A patient may have had a 50% increase from baseline in serum creatinine, but remained within the normal range
†Out of the 15 patients, there were 12 reports of acute renal failure and 3 of renal failure
MedDRA, medical dictionary for regulatory activities

CONCLUSIONS

- Telavancin, administered once daily, produced positive clinical outcomes in the majority of patients (119/174, 68.4%) treated for bone and joint infections
- Telavancin was frequently administered in an outpatient setting, primarily used as a second-line therapy at a median average daily dose of 8.7 mg/kg, median total daily dose of 750 mg, and for a median of 26 days
- The AEs were similar to those reported in other TLV clinical trials
- With these preliminary data, once-daily TLV achieved positive clinical success rates in patients with bone and joint infections, and may represent an effective alternative treatment option (completed TOUR data will be available and reported at a later date)

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