Poster #2369

Clinical Experience with Telavancin for Treatment of Patients with Monomicrobial *S. aureus* Infections (Vancomycin MIC ≥1 µg/mL) from TOUR™

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INTRODUCTION

- Telavancin (TLV) is a lipoglycopeptide antibacterial active against susceptible Gram-positive pathogens, including methicillin-susceptible and -resistant *Staphylococcus aureus* (*S. aureus*; MSSA and MRSA), administered intravenously once-daily and is suitable for both inpatient and outpatient use[1-3]
- In the US, TLV is approved in adults for the treatment of complicated skin and skin structure infections (cSSSI) due to susceptible Gram-positive pathogens and for hospital-acquired and ventilator-associated bacterial pneumonia when alternative treatments are not suitable[1]
- TLV is also approved for use in Canada, Israel, and Russia for specific indications,[*4-7] and in the EU on a named-patient basis
- The Telavancin Observational Use Registry (TOUR™) is a US multicenter, retrospective chart review study designed to determine the real-world efficacy of TLV and characterize infection types, pathogens, and outcomes of patients treated with TLV in clinical practice
- Infections due to *S. aureus* with elevated vancomycin (VAN) minimum inhibitory concentration (MIC) values are associated with worse clinical outcomes relative to *S. aureus* infections with lower VAN MIC[8]
- To better understand the role of TLV in treatment of *S. aureus* infections with elevated VAN MIC, we analyzed real-world data including patient demographics, infecting pathogens, TLV treatment outcomes, and adverse events (AEs) in patients with monomicrobial *S. aureus* infections with VAN MIC ≥1 µg/mL from TOUR™

METHODS

TOUR™ Registry Methodology and Design

- TOUR™ collected real-world data on 1063 patients from 45 US hospitals or outpatient infusion centers between January 2015 and March 2017
- 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; data were obtained via retrospective medical chart review

Data Collection and Analyses

- Data from TOUR™ were used to focus on a subset of patients with monomicrobial infections due to *S. aureus* with VAN MIC ≥1 µg/mL
- Demographics, primary infection type, baseline pathogens, setting of hospitalization, prior or concomitant antimicrobial treatment, TLV dosing, clinical response, and AEs were entered directly into electronic case report forms and analyzed using descriptive statistics
- Adverse event data collection was limited to renal AEs and AEs leading to discontinuation or a fatal outcome
- Clinical outcomes were determined by investigator assessment and categorized as positive (clinical cure or improvement to step-down oral therapy), indeterminate, or failed
- Creatinine clearance was estimated by Cockcroft-Gault using actual body weight for all patients with serum creatinine measurements at baseline

RESULTS

- TOUR™ enrolled a total of 1063 patients from 45 sites; monomicrobial *S. aureus* with VAN MIC ≥1 µg/mL was isolated from 159 patients
- The majority of patients in this subset were White (84.9%), male (60.4%), and <65 years of age (74.2%) (**Table 1**); the most frequent comorbidities were hypertension (37.1%), type 2 diabetes mellitus (29.6%), and drug abuse (15.1%) (**Table 2**)
- The most frequent primary infection type was cSSSI (45.9%), followed by bacteremia and endocarditis (28.9%), bone and joint infection (15.7%), and lower respiratory infection (13.2%) (**Table 1**)
- The *S. aureus* isolate was MRSA in 77.4% of patients and MSSA in 22.6% of patients (**Table 3**)
- The majority of isolates (65.4%) had VAN MIC of 1.0 µg/mL, 32.1% of patients had *S. aureus* with VAN MIC of 2.0 µg/mL, and VAN susceptibility was similar between MRSA and MSSA isolates (**Table 3**); the most frequently used VAN susceptibility tests were Microscan (46.5%), VITEK (28.3%), and Etest (4.4%)
- TLV was second-line or greater therapy in 123/159 patients (77.4%); 70/159 patients (44.0%) received VAN prior to TLV treatment, and 35/159 (22.0%) patients received >1 antibiotic before TLV treatment (**Table 4**)
- TLV dose was chosen by the treating physician; patients received a median of 8.5 mg/kg (interquartile range [IQR]: 7.4, 9.9 mg/kg) of TLV for a median of 8 days (IQR: 3, 17 days), and TLV dosing was not adjusted during therapy in most (91.8%) patients (**Table 5**)
- The majority of patients initiated TLV therapy as inpatients (hospital ward, 58.5%; intensive care unit, 11.9%). Among 106 patients with hospital discharge data, median time to discharge was 7 days (IQR: 3, 13 days) after starting TLV; 41.5% of patients were discharged to home, and 21.4% of patients continued TLV as outpatients (**Table 6**)
- Of the 144 patients with available response assessment at end of TLV treatment, 77.1% had a positive clinical response, defined as cure or improvement to step-down oral therapy, following TLV therapy; the majority of patients had a positive clinical response across all infection types (**Figure 1**) and VAN MIC categories (**Table 7**)
- A total of 17 (10.7%) patients reported treatment-emergent AEs, including 9 serious AEs, 10 AEs considered possibly related to TLV, 12 AEs leading to TLV discontinuation, and 10 AEs that resolved (**Table 8**); 7 AEs led to a fatal outcome
- Renal failure AEs occurred in 7 (4.4%) patients and resolved in 6 patients (**Table 8**)

Table 1. Baseline Demographics and Clinical Characteristics of Patients with Infections Due to Monomicrobial *S. aureus* with VAN MIC ≥1 µg/mL

Characteristic	N = 159
Age (years)	
Mean (SD)	51.9 (17.1)
Median (IQR)	54.0 (40.0, 65.0)
Age distribution, n (%)*	
<65	118 (74.2)
≥65	41 (25.8)
≥75	17 (10.7)
Sex, n (%)	
Male	96 (60.4)
Female	63 (39.6)
Ethnicity, n (%)	
Hispanic or Latino	8 (5.0)
Not Hispanic or Latino	149 (93.7)
Not reported	2 (1.3)
Race, n (%)	
American Indian or Alaskan Native	3 (1.9)
Asian	2 (1.3)
Black or African American	16 (10.1)
Native Hawaiian or other Pacific Islander	0
White	135 (84.9)
Other	3 (1.9)
BMI (kg/m²)	
Mean (SD)	29.3 (10.1)
Median (IQR)	27.5 (22.9, 33.9)
Baseline CrCl, n (%)	
<30 mL/min	1 (0.6)
30–<50 mL/min	11 (6.9)
50–<80 mL/min	19 (11.9)
≥80 mL/min	97 (61.0)
Missing	31 (19.5)
Dialysis, n (%)	
No	149 (93.7)
Yes	10 (6.3)
Type of infection at baseline, n (%)†	
cSSSI	73 (45.9)
Bacteremia and endocarditis	46 (28.9)
Bone and joint infections	25 (15.7)
Lower respiratory infection	21 (13.2)

*% of total population (N = 159) for all age categories, ≥65 category is inclusive of ≥75 category; †Infection groups are not all-inclusive or mutually exclusive.
BMI, body mass index; CrCl, creatinine clearance; cSSSI, complicated skin and skin structure infections; IQR, interquartile range; MIC, minimum inhibitory concentration; *S. aureus*, *Staphylococcus aureus*; SD, standard deviation; VAN, vancomycin.

Table 2. Baseline Comorbid Conditions in >10% of Patients with Infections Due to Monomicrobial *S. aureus* with VAN MIC ≥1 µg/mL

Comorbidities	N = 159 n (%)*
Hypertension	59 (37.1)
Type 2 diabetes mellitus	47 (29.6)
Drug abuse	24 (15.1)
Myocardial infarction	23 (14.5)
COPD	20 (12.6)
Renal failure, chronic	19 (11.9)
Cardiac failure, congestive	16 (10.1)

*Some patients had multiple comorbidities.
COPD, chronic obstructive pulmonary disease; MIC, minimum inhibitory concentration; *S. aureus*, *Staphylococcus aureus*; VAN, vancomycin.

Table 3. Baseline Infecting Pathogens in Patients with Infections Due to Monomicrobial *S. aureus* with VAN MIC ≥1 µg/mL by VAN MIC*

VAN MIC (µg/mL)	MRSA	MSSA	Total (N = 159)
All, n (%)	123 (77.4)	36 (22.6)	159 (100.0)
1.0	80 (65.0)†	24 (66.7)†	104 (65.4)
1.5	4 (3.3)†	0	4 (2.5)
2.0	39 (31.7)†	12 (33.3)†	51 (32.1)
>2.0	0	0	0

*VAN MIC determined by Microsan (46.5%), VITEK (28.3%), or Etest (4.4%) in most cases; †Percentage based on n = 123 patients with MRSA; ‡Percentage based on n = 36 patients with MSSA.
MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; *S. aureus*, *Staphylococcus aureus*; VAN, vancomycin.

Table 4. Prior Antibiotics* Administered in >2% of Patients with Infections Due to Monomicrobial *S. aureus* with VAN MIC ≥1 µg/mL

WHO Generic Name	N = 159 n (%)
Vancomycin	70 (44.0)
Piperacillin + tazobactam	12 (7.5)
Daptomycin	11 (6.9)
Clindamycin	9 (5.7)
Sulfamethoxazole + trimethoprim	9 (5.7)
Ceftriaxone	8 (5.0)
Cefazolin	7 (4.4)
Ceftaroline	5 (3.1)
Linezolid	4 (2.5)

*35 patients received >1 prior antibiotic.
MIC, minimum inhibitory concentration; *S. aureus*, *Staphylococcus aureus*; VAN, vancomycin; WHO, World Health Organization.

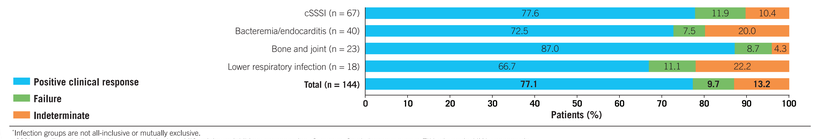
Table 5. TLV Dosing by Baseline Creatinine Clearance and Average Daily Dose Category in Patients with Infections Due to Monomicrobial *S. aureus* with VAN MIC ≥1 µg/mL

	Baseline CrCl (mL/min)					
TLV Exposure Characteristics	Dialysis (n = 10)	<30 (n = 1)	30–<50 (n = 11)	50–<80 (n = 19)	≥80 (n = 97)	Total (N = 159)*
Average daily dose† (mg)						
Mean (SD)	534.6 (263.8)	500.0 (N/A)	565.1 (209.4)	692.1 (139.4)	753.3 (213.0)	712.9 (214.2)
Median (IQR)	438.7 (336.2, 700.0)	500.0 (N/A)	510.0 (450.0, 701.6)	750.0 (600.0, 750.0)	750.0 (727.3, 750.0)	750.0 (575.0, 750.0)
Treatment duration (days)						
Mean (SD)	29.7 (19.6)	2.0 (N/A)	19.9 (23.9)	8.6 (10.3)	14.8 (22.9)	15.2 (20.9)
Median (IQR)	25.5 (12, 43)	2 (N/A)	5 (2, 45)	5 (3, 10)	8 (3, 15)	8 (3, 17)
Average daily dose per bodyweight (mg/kg)						
Mean (SD)	5.9 (2.7)	10.0 (N/A)	7.7 (1.4)	8.9 (1.4)	8.6 (1.7)	8.5 (2.0)
Median (IQR)	4.9 (4.3, 7.2)	10.0 (N/A)	7.6 (6.8, 8.7)	8.8 (8.1, 10.0)	8.5 (7.4, 9.8)	8.5 (7.4, 9.9)
TLV dose adjusted, n (%)						
Yes	2 (20.0)	0	2 (18.2)	1 (5.3)	8 (8.2)	13 (8.2)
No	8 (80.0)	1 (100.0)	9 (81.8)	18 (94.7)	89 (91.8)	146 (91.8)

	TLV Average Daily Dose (mg) (N = 159)				
	<750	750	>750–<1000	1000	>1000
Patients, n (%)	58 (36.5)	79 (49.7)	8 (5.0)	9 (5.7)	5 (3.1)

*Baseline CrCl-based TLV dosing was not estimated for 21 patients due to missing data; †Average dose per 24-hour period in patients dosed at 48-hour intervals.
CrCl, creatinine clearance; IQR, interquartile range; MIC, minimum inhibitory concentration; N/A, not applicable; *S. aureus*, *Staphylococcus aureus*; SD, standard deviation; TLV, telavancin; VAN, vancomycin.

Figure 1. Clinical Outcomes for Patients with Available Outcome Assessment at End of TLV Treatment by Infection Type in Patients with Infections Due to Monomicrobial *S. aureus* with VAN MIC ≥1 µg/mL*



*Infection groups are not all-inclusive or mutually exclusive.
cSSSI, complicated skin and skin structure infections; MIC, minimum inhibitory concentration; *S. aureus*, *Staphylococcus aureus*; TLV, telavancin; VAN, vancomycin.

Table 6. Patient Care Setting at TLV Initiation and Length of Hospitalization in Patients with Infections Due to Monomicrobial *S. aureus* with VAN MIC ≥1 µg/mL

Care Setting Parameter	N = 159
Setting at TLV initiation, n (%)	
Hospital ward	93 (58.5)
ICU	19 (11.9)
Emergency department	2 (1.3)
Outpatient infusion center	23 (14.5)
Outpatient clinic	22 (13.8)
Total days of hospitalization*	
Mean (SD)	16.7 (28.1)
Median (IQR)	8 (5, 18)
Days to hospital discharge†	
Mean (SD)	11.0 (14.4)
Median (IQR)	7 (3, 13)
Discharge location, n (%)	
Home	66 (41.5)
Other	19 (11.9)
Nursing home	17 (10.7)
Hospice	2 (1.3)
Unknown	2 (1.3)
Continued TLV as outpatient, n (%)	
Yes	34 (21.4)
No	79 (49.7)
Unknown	1 (0.6)

*n = 122, includes time before initiation of TLV; †n = 106, time from initiation of TLV to hospital discharge.
ICU, intensive care unit; IQR, interquartile range; MIC, minimum inhibitory concentration; *S. aureus*, *Staphylococcus aureus*; SD, standard deviation; TLV, telavancin; VAN, vancomycin.

Table 7. Clinical Outcomes for Patients with Available Outcome Assessment at EOT (n = 144) by VAN MIC in Patients with Infections Due to Monomicrobial *S. aureus* with VAN MIC ≥1 µg/mL

	Clinical Outcome, n (%)		
VAN MIC (µg/mL)	Positive Clinical Response	Failed Treatment	Indeterminate
1.0	74 (78.7)	9 (9.6)	11 (11.7)
1.5	2 (50.0)	0	2 (50.0)
2.0	35 (76.1)	5 (10.9)	6 (13.0)
Total	111 (77.1)	14 (9.7)	19 (13.2)

EOT, end of treatment; MIC, minimum inhibitory concentration; *S. aureus*, *Staphylococcus aureus*; VAN, vancomycin.

Table 8. All Reported Treatment-Emergent AEs of Interest in Patients with Infections Due to Monomicrobial *S. aureus* with VAN MIC ≥1 µg/mL*

MedDRA Preferred Term	Frequency n (%)	Serious n (%)	Possibly Related to Treatment n (%)	Discontinued Treatment† n (%)	Resolved‡ n (%)
Renal failure§	7 (4.4)	3 (1.9)	6 (3.8)	5 (3.1)	6 (3.8)
Respiratory failure	4 (2.5)	4 (2.5)	0	4 (2.5)	0
Nausea	3 (1.9)	0	3 (1.9)	3 (1.9)	3 (1.9)
Vomiting	2 (1.3)	0	2 (1.3)	2 (1.3)	2 (1.3)
Cardiac failure congestive	1 (0.6)	1 (0.6)	0	0	0
Death	1 (0.6)	1 (0.6)	0	0	0
Drug intolerance	1 (0.6)	0	1 (0.6)	1 (0.6)	1 (0.6)
Sepsis	1 (0.6)	1 (0.6)	0	1 (0.6)	0

*AEs of interest were limited to renal AEs, AEs leading to discontinuation of TLV, and fatal AEs; †Discontinued treatment includes patients who had drug withdrawn or withdrew from the study; ‡Resolved includes AEs recorded as Recovered/Resolved, Recovered/Resolved with Sequelae, or Recovering/Resolving; §Renal failure includes MedDRA preferred terms "renal failure" and "renal failure acute".
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; MIC, minimum inhibitory concentration; *S. aureus*, *Staphylococcus aureus*; TLV, telavancin; VAN, vancomycin.

CONCLUSIONS

- TLV produced positive clinical outcomes in the majority of patients with available outcome assessment at end of treatment for a variety of infection types due to *S. aureus* with VAN MIC ≥1 µg/mL
- Once-daily TLV was used primarily as second-line or greater therapy, most often following VAN, at a median dose of 8.5 mg/kg for a median of 8 days; the majority of patients in this subset started TLV treatment in inpatient settings
- No new safety signals were identified in this patient subset; 4.4% of this subset reported renal failure, and the majority of these cases were reported as resolved
- Limitations inherent to the observational design of TOUR™ include potential patient selection bias, subjective outcome assessments, potential outcome bias due to missing outcome assessments, and site-to-site variation in data collection
- These real-world data demonstrate that once-daily TLV achieved positive clinical responses in the majority of patients with infections due to *S. aureus* with elevated VAN MIC and may represent an alternative treatment option for such infections

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*In Canada and Russia, TLV is approved for the treatment of patients with Gram-positive cSSSI and HABP/VABP.[4,5] In Israel, TLV is approved for the treatment of adults with nosocomial pneumonia including VABP, known or suspected to be caused by MRSA. TLV should be used only in situations where it is known or suspected that other alternatives are not suitable.[6] The marketing authorization in the EU was voluntarily withdrawn by the manufacturer due to low use of TLV.[7]

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