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Telavancin for refractory MRSA bacteraemia in intermittent haemodialysis recipients

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Background: Patients with end-stage renal disease (ESRD) requiring intermittent haemodialysis (IHD) are at high risk of MRSA bacteraemia (MRSA-B) and often fail first-line therapy. The safety, effectiveness and optimal dosing of telavancin for MRSA-B in this patient population are unclear.

Objectives: We aimed to describe clinical outcomes of telavancin in the treatment of refractory MRSA-B in patients with ESRD requiring IHD.

Patients and methods: This was a retrospective study of hospitalized patients at two tertiary care academic medical centres with recurrent or persistent (≥3 days) MRSA-B treated with telavancin monotherapy. Outcomes included duration of MRSA-B (pre-telavancin versus post-telavancin) and microbiological failure (duration of MRSA-B ≥3 days after initiation of telavancin).

Results: Telavancin dosed 10 mg/kg three times weekly post-IHD or 10 mg/kg every 48 h resulted in microbiological cure in 7/8 (87.5%) refractory MRSA-B cases. Telavancin monotherapy was associated with a significant reduction in median duration of bacteraemia [16 days pre-telavancin (IQR 8–19 days) versus 1 day post-telavancin (IQR 0–2 days); $P = 0.018$]. Telavancin was well tolerated by all patients and no adverse events were reported.

Conclusions: Telavancin was very safe and highly effective in the treatment of refractory MRSA-B in a cohort of patients with ESRD requiring IHD. These data support the utility of telavancin in the armamentarium against refractory MRSA-B, particularly in the high-risk IHD-dependent population.

Introduction

MRSA bacteraemia (MRSA-B) is associated with significant morbidity and mortality.[1,2] Vancomycin is the mainstay of MRSA-B treatment, but failures are common and the optimal therapy for persistent infection is uncertain.[1,3] Telavancin is a lipoglycopeptide antibiotic with a dual mechanism of action that exhibits potent bactericidal activity against MRSA, including strains with reduced susceptibility to vancomycin or daptomycin.[4] Despite this favourable antibacterial profile, there are limited data describing the utility of telavancin as a treatment option for MRSA-B.[5] Patients with end-stage renal disease (ESRD) receiving intermittent haemodialysis (IHD) are at increased risk of developing MRSA-B and often fail first-line therapy.[2] Clinical experience using telavancin in the treatment of MRSA-B in this high-risk patient population is limited. Although data regarding the optimal dosing strategy are limited, telavancin may be an effective option in the treatment of MRSA-B in this difficult-to-manage patient population. This study describes the consecutive use of telavancin in the treatment of refractory MRSA-B among IHD recipients.

Patients and methods

Ethics

This study was conducted in accordance with the Declaration of Helsinki and was approved with waivers of informed consent by institutional review boards at the Washington University in St Louis and Yale-New Haven Hospital.

Study design and clinical outcomes

This was a multicentre retrospective study performed at Barnes-Jewish Hospital (St Louis, MO, USA) and Yale-New Haven Hospital (New Haven, CT, USA). We included hospitalized ESRD patients requiring IHD with persistent ($\geq$3 days) or recurrent MRSA-B failing one or more anti-MRSA agents.[3] Clinical outcomes evaluated included duration of MRSA-B pre-telavancin versus post-telavancin (compared by Wilcoxon signed rank tested), microbiological failure and 30 day all-cause mortality. Microbiological failure was defined as duration of MRSA-B $\geq$3 days following initiation of telavancin. Statistical analyses were performed using SPSS (version 23, IBM Corporation, Armonk, NY, USA) and $P < 0.05$ was considered statistically significant.

Susceptibility testing

.Telavancin MIC testing was performed by broth microdilution at The Theravance Reference Laboratory (Laboratory Specialists, Inc., Westlake, OH, USA) according to CLSI recommendations.[6] All other susceptibility testing occurred during routine clinical care according to institutional procedures.

Results

Case reports and clinical outcomes

A total of eight cases were identified for inclusion and corresponding clinical descriptions are summarized in Table 1.

Case 1 occurred in a 59-year-old female presenting with recurrent MRSA-B after a 4 week course of daptomycin 6 mg/kg completed ~1 month prior to admission. Owing to concerns regarding previous daptomycin failure and elevated vancomycin MIC, telavancin was initiated and blood cultures cleared the following day. The patient tolerated telavancin well and was discharged to complete 6 weeks of therapy followed by chronic oral suppressive doxycycline due to retained graft material.

Case 2 occurred in a 69-year-old female who presented from an outside hospital with recurrent MRSA-B. The previous episode was treated with a 6 week course of vancomycin completed ~1.5 months prior to admission to the outside hospital. For the present episode, vancomycin was restarted; however, after 9 days of persistent MRSA-B, imaging showed discitis of the 10th and 11th thoracic intervertebral spaces. The patient was then transferred to a study site hospital and switched to daptomycin 6 mg/kg. After 16 days of persistent MRSA-B, the patient was switched to telavancin and blood cultures cleared after 1 day of therapy.

Case 3 occurred in a 47-year-old female with MRSA-B. Vancomycin was initiated, but after 3 days of persistent MRSA-B, the patient was switched to telavancin owing to concerns for vancomycin failure in the setting of elevated vancomycin MIC. The patient tolerated telavancin well and follow-up blood cultures after telavancin initiation were negative.

Case 4 occurred in a 55-year-old female admitted from an outside hospital with persistent MRSA-B and mitral valve endocarditis. The patient received vancomycin for ~2 weeks, followed by 5 days of daptomycin 6 mg/kg. Upon transfer, the corresponding MRSA blood isolate was vancomycin intermediate/daptomycin non-susceptible and telavancin was initiated. She underwent mitral valve replacement, follow-up blood cultures were negative and 6 weeks of telavancin were completed.

Case 5 occurred in a 58-year-old male admitted for recurrent MRSA-B. The patient was admitted ~1.5 months previously with MRSA-B and treated with a 2 week course of vancomycin. The patient was restarted on vancomycin; however, MRSA-B persisted and the arteriovenous graft was excised. Despite surgical intervention, blood cultures remained persistently positive, and on hospital day 8 the patient was switched to telavancin. The patient's blood cultures cleared 1 day later and an additional 4 weeks of telavancin were completed.

Case 6 occurred in a 74-year-old female presenting with MRSA-B that was initially managed with vancomycin. After 10 days of persistent MRSA-B, the patient was transitioned to telavancin and underwent partial arteriovenous graft excision. The patient tolerated telavancin well and all follow-up blood cultures were negative.

Case 7 occurred in an 85-year-old male with MRSA-B admitted from a nursing home. Blood cultures remained persistently positive up to hospital day 10, at which point the patient received one dose of linezolid and was switched to daptomycin 6 mg/kg. MRSA-B persisted and telavancin was initiated. On hospital day 29, the patient remained bacteraemic and was switched to ceftaroline. Blood cultures subsequently were negative after 1 day of ceftaroline. On hospital day 53, the patient decompensated and was ultimately transitioned to comfort care.

Case 8 occurred in a 61-year-old female admitted for recurrent MRSA-B. The patient was treated for 2 weeks with vancomycin and subsequently switched to daptomycin 6 mg/kg. Ceftaroline was added to daptomycin on hospital day 10 owing to persistent MRSA-B. Daptomycin was later discontinued due to development of eosinophilia and the patient commenced on vancomycin/ceftaroline combination therapy. The patient remained persistently bacteraemic and was transferred to a study site hospital. Upon arrival, the patient was transitioned to telavancin monotherapy. Follow-up blood cultures were negative.

Microbiological outcomes

Among persistent MRSA-B cases, the median duration of bacteraemia was 16 days (IQR 8–19 days) pre-telavancin and 1 day (IQR 0–2 days) post-telavancin ($P = 0.018$). One case of microbiological failure of telavancin was observed (Case 7).

Discussion

We report the successful use of telavancin in 7/8 cases (87.5%) of refractory MRSA-B failing first-line therapy in the setting of ESRD requiring IHD. Microbiological response was rapid and all patients who responded to telavancin therapy cleared MRSA-B within 2 days of telavancin initiation. The mechanism for this rapid response may be the potent bactericidal activity of telavancin against MRSA and a prolonged duration of action in the setting of ESRD. Telavancin may also synergize with important innate immune system components, such as the host defence peptide human cathelicidin LL-37, against certain MRSA-B isolates (data on file with G. S. and V. N.). In the haemodialysis population, host

Table 1. Summary of refractory MRSA bacteraemia cases in IHD-dependent patients treated with telavancin monotherapy

Case	MRSA bacteraemia		MIC (mg/L)[a]	TLV dosing regimen	Disease severity and comorbidity indices	Diagnostic findings	Days positive		Surgical intervention	Microbiological failure[b]	30 day mortality
	classification	source					pre-TLV	post-TLV			
1	recurrent (failed DAP)	AV graft	VAN, 2 DAP, 1	10 mg/kg three times weekly	CCI, 9 PBS, 0 APACHE II, 8	TTE, negative TEE, negative	1	0	AV graft excision (partial, day 4)	no	no
2	recurrent, persistent (failed VAN, DAP)	AV graft	VAN, 2 DAP, 1	10 mg/kg three times weekly	CCI, 9 PBS, 1 APACHE II, 13	TTE, negative T10/11 discitis	16	1	AV graft excision (day 2), laminectomy/spinal cord decompression (day 28)	no	no
3	persistent (failed VAN)	AV fistula	VAN, 2 DAP, 0.5	10 mg/kg three times weekly	CCI, 7 PBS, 1 APACHE II, 14	TTE, negative TEE, negative	3	0	–	no	no
4	persistent (failed VAN, DAP)	MV IE	VAN, ≥4[c] DAP, ≥2[c] TLV, 0.12	10 mg/kg three times weekly	CCI, 5 PBS, 1 APACHE II, 11	TEE, 4.8 cm vegetation	19	0	MV replacement (day 19)	no	no
5	recurrent, persistent (failed VAN)	AV graft	VAN, 2 DAP, 1	10 mg/kg three times weekly	CCI, 7 PBS, 1 APACHE II, 17	TTE, negative TEE, negative CT, pulmonary nodules	8	1	AV graft excision (day 6)	no	no
6	persistent (failed VAN)	AV graft	VAN, 0.5 DAP, 0.75 TLV, 0.06 CPT, 0.75	10 mg/kg q48h[d]	CCI, 12 PBS, 1 APACHE II, 18	TTE, negative	10	2	AV graft excision (partial, day 11)	no	no
7	persistent (failed VAN, DAP)	AV graft	VAN, 2 DAP, 0.75 TLV, 0.06	10 mg/kg q48h	CCI, 12 PBS, 2 APACHE II, 17	TTE, negative TEE, negative	19	11	AV graft excision (day 15)	yes	yes
8	recurrent, persistent (failed VAN, DAP)	AV graft, pacemaker	VAN, 2	10 mg/kg q48h[d]	CCI, 6 PBS, 0 APACHE II, 20	TTE, negative TEE, negative	20	1	AV graft excision (day 1), pacemaker removal (day 27)	no	no

CCI, Charlson comorbidity index; PBS, Pitt bacteraemia score; TLV, telavancin; DAP, daptomycin; AV, arteriovenous; VAN, vancomycin; TTE, transthoracic echocardiography; TEE, transoesophageal echocardiography; T, thoracic; MV, mitral valve; IE, infective endocarditis; CPT, ceftaroline.

[a]All telavancin MICs were determined by broth microdilution; all other MICs were determined by Etest (bioMérieux, Marcy-l'Étoile, France) unless otherwise indicated.

[b]Duration of MRSA bacteraemia ≥3 days after telavancin initiation.

[c]By disc diffusion method.

[d]Transitioned to outpatient three times weekly dosing post-haemodialysis.

defence peptides have been shown to have an important influence on outcomes and low plasma concentrations correspond to an increased risk of infection-related mortality.[7] Future research exploring the pharmacodynamic interaction between telavancin and innate immune system components is warranted.

Telavancin holds a boxed warning for nephrotoxicity, yet this adverse effect is not clinically significant when used for serious MRSA infections in the setting of ESRD.[4] Telavancin primarily undergoes renal elimination, though there are currently no recommendations for dosing in patients requiring three-times-weekly IHD.[4] In the present study, doses of 10 mg/kg every 48 h or 10 mg/kg post-haemodialysis three times weekly were used according to institutional practices. The doses selected were supported by limited pharmacokinetic data and reflect those used in Phase 3 clinical trials.[8] The high percentage of clinical success and lack of adverse events observed in the present study provide the most compelling evidence to date supporting the effectiveness and safety of telavancin for MRSA-B in this vulnerable patient population.

This study featured a small sample and a relatively heterogeneous population. Owing to the retrospective nature of this investigation and lack of comparator, we cannot definitively conclude that telavancin alone was responsible for the outcomes observed. The cases included differed in their durations of MRSA-B, organism susceptibility patterns and source control prior to telavancin therapy. Nonetheless, this study provides important and novel information supporting the effectiveness and safety of telavancin in the setting of recalcitrant MRSA-B, particularly in the high-risk IHD-dependent population.

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Transparency declarations

N. S. B. has served as a consultant on research grants from Merck & Co. and Gilead Sciences. D. J. R. has received speaking honoraria from Allergan, Astellas Pharma and Theravance Biopharma. V. N. has received research grant support from Roche Pharma and is on the Scientific Advisory Board of Cidara Therapeutics. G. S. has received speaking honoraria from Allergan, Theravance Biopharma and The Medicines Company, and consulting fees from Allergan. All other authors: none to declare.

References

1 Liu C, Bayer A, Cosgrove SE *et al*. Clinical practice guidelines by the Infectious Diseases Society Of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* 2011; **52**: e18–55.

2 van Hal SJ, Jensen SO, Vaska VL *et al*. Predictors of mortality in *Staphylococcus aureus* bacteremia. *Clin Microbiol Rev* 2012; **25**: 362–86.

3 Kullar R, McKinnell JA, Sakoulas G. Avoiding the perfect storm: the biologic and clinical case for reevaluating the 7-day expectation for methicillin-resistant *Staphylococcus aureus* bacteremia before switching therapy. *Clin Infect Dis* 2014; **59**: 1455–61.

4 *Vibativ (Telavancin for Injection) [Package Insert]*. Deerfield, IN, USA: Astellas Pharma US, Inc., 2009.

5 Ruggero MA, Peaper DR, Topal JE. Telavancin for refractory methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis. *Infect Dis (Lond)* 2015; **47**: 379–84.

6 Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing: Twenty-Sixth Informational Supplement M100-S26*. CLSI, Wayne, PA, USA, 2016.

7 Gombart AF, Bhan I, Borregaard N *et al*. Low plasma level of cathelicidin antimicrobial peptide (hCAP18) predicts increased infectious disease mortality in patients undergoing hemodialysis. *Clin Infect Dis* 2009; **48**: 418–24.

8 Gharibian KN, Lewis SJ, Heung M *et al*. Telavancin pharmacokinetics in patients with chronic kidney disease receiving hemodialysis. In: *Abstracts of the 2016 American College of Clinical Pharmacy Annual Meeting, Hollywood, FL, USA, 2016*. Abstract 207. American College of Clinical Pharmacy, Lenexa, KS, USA.