Research Article

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Experience with Telavancin for Treatment of Methicillin-Resistant Staphylococcus Aureus (MRSA) Endocarditis

Lindsay Jablonski, Byungse Suh*

Section of Infectious Diseases, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania 19140, USA

Corresponding author: Byungse Suh, Section of Infectious Diseases, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania 19140, USA. Tel : 215-707-3603, E-mail: bingsoh@temple.edu

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Running title: Telavancin Efficacy Against Methicillin-Resistant S. Aureus

Abstract :

Complicated methicillin-resistant Staphylococcus aureus (MRSA) bacteremia is becoming increasingly challenging to manage. We have noted that many patients have a poor response to vancomycin and daptomycin, which are the first-line agents recommended by the Infectious Diseases Society of America (IDSA) guidelines for the treatment of MRSA bacteremia. Telavancin has been approved for complicated skin and skin-structure infections and hospital-acquired and ventilator-associated bacterial pneumonia including those with concomitant bacteremia. We analyzed 8 patients with MRSA bacteremia with or without infective endocarditis who were treated with telavancin. Seven out of 8 patients treated for refractory bacteremia had blood cultures cleared on telavancin therapy. One patient died after receiving telavancin for 2 days, soon after cardiac surgery. Five of 8 (62.5%) patients had definite infective endocarditis (IE), 2 had possible IE by modified Duke's Criteria. No patient developed renal failure necessitating a change in antibiotic therapy. While more randomized controlled clinical trials need to be conducted, telavancin may be useful in the management of MRSA endocarditis, and may be especially helpful for patients who have failed first-line therapy.

Introduction:

In our 500 bed urban hospital, we have noticed a rising number of cases of persistent methicillin-resistant Staphylococcus aureus (MRSA) bacteremia that did not clear with vancomycin even when we could document acceptable vancomycin troughs and MICs < 2 µg/ml. In this retrospective case series, 8 patients received telavancin for the treatment of MRSA bacteremia after failure of either or both vancomycin and daptomycin therapy.

Telavancin is a semisynthetic lipoglycopeptide antibiotic with potent bactericidal activity against most gram-positive human pathogens including MRSA. It has a dual mechanism of action, involving inhibition of cell wall synthesis through a mechanism similar to that of vancomycin, as well as depolarization of cell membranes leading to cell death. It was first approved in 2009 for complicated skin and skin-structure infections (cSSSI), and more recently in 2013 it received additional approval for treating hospital-acquired

bacterial and ventilator-associated bacterial pneumonias (HABP/VABP) caused by susceptible gram-positive bacteria, including MRSA. It is now has expanded FDA-approval, including concurrent bacteremia in patients with cSSSI and HABP/VABP. The MIC breakpoint for telavancin against S. aureus has also been revised to ≤0.12 µg/ml (Wenzler et al. 2015). This dual mechanism of action has shown improved bactericidal activity over that of vancomycin in vitro (Lunde et al. 2009).

The most recent IDSA guidelines for the treatment of MRSA bacteremia and native valve infective endocarditis (IE) recommend vancomycin or daptomycin as first line therapy (Liu et al. 2011). There has been correlation of daptomycin resistance with vancomycin-intermediate S. aureus (VISA) and hVISA (Cui et al. 2006). An increase of MICs to vancomycin and daptomycin despite adequate serum drug levels has also been described, along with high

rates of clinical failure for bacteremia for both drugs (Fowler et al. 2006). Telavancin is often thought of as salvage therapy for refractory bacteremia (Kullar et al. 2016). Theravance is current-

ly conducting a Phase 3 trial studying the use of telavancin for treatment of complicated S. aureus bacteremia including infective endocarditis.

Table1. Patient characteristics and outcomes

Case No.	Age	Likely etiology of bacteremia	IE	Days of MRSA bacteremia	Days on vancomycin	Vancomycin MIC	Days on daptomycin	Daptomycin MIC	Reason for change to telavancin	Telavancin MIC	Days to culture clearance on telavancin	Days on telavancin	Survival to hospital discharge
1	54	AV graft for HD	Yes	9	0	2	8	NR	Persistent bacteremia	0.25	--	2	No
2	75	PICC	Yes	7	7	1	3	1.5	Persistent bacteremia	NR	--	2-9*	Yes
3	41	IVDA	No	Intermittent	8	1→2	24	≤1	Fever on daptomycin	NR	--	16	Yes
4	50	IVDA	Yes	16	6	≤0.5→2	14	1.5	Persistent bacteremia	0.5	--	29	Yes
5	38	IVDA	Possible	Intermittent	8	1	0	≤1	Persistent bacteremia	NR	--	29	Yes
6	25	IVDA	Yes	9	8	1	16	≤1	Fever on daptomycin	NR	--	11	Yes
7	37	IVDA	Yes	Intermittent	11	≤0.5→1	0	≤1	Persistent bacteremia	NR	3	30	Yes
8	20	Unknown	Possible	7	3	1	4	≤1	Persistent bacteremia	NR	1	32	Yes

IE = Infective endocarditis. IE was defined by Modified Duke's Criteria; NR=Not Reported; PICC = Peripherally Inserted central venous catheter. IVDA = Intravenous drug abuse;

-- = Blood cultures had already cleared at the time telavancin was initiated;

* = Unclear timeline of telavancin administration. Patient was discharged after 2 days of therapy, readmitted 7 days later with unclear administration history during time out of hospital.

Materials and Methods:

Design and Setting:

A list was generated from the pharmacy computer of all patients who received telavancin between November 24, 2009 and February 21, 2016. All patients with documented blood cultures positive for MRSA with and without IE were selected from this list to be included in this series. This study was approved by the Institutional Review Board at Temple University.

Inclusion and definitions:

Of the 12 patients who had received at least one dose of telavancin during the time period specified, 8 patients had documented MRSA bacteremia and were included in the series. Patients who were excluded received telavancin for methicillin-susceptible S. aureus or methicillin-resistant S. epidermidis. Medical records were reviewed, and data including age, comorbidities, blood culture results, antibiotic usage, clinical outcomes, and survival to the time of discharge were collected. Attempts were made to ascertain the most likely etiology of bacteremia for each patient (i.e. venous

catheter, intravenous drug abuse) and whether or not IE was present defined by Duke's Criteria.

Results:

Baseline characteristics:

The median age was 39 years (range 20-75 years). Five patients were male and 3 were female. One patient had a documented history of chronic kidney disease, and one patient had end-stage renal disease requiring hemodialysis prior to admission. Five patients had a history of intravenous drug abuse (IVDA). Two patients had indwelling vascular catheters prior to admission.

Clinical outcomes:

Over half of the patients had an active history of IVDA suggesting they likely had acquired MRSA infection from the community. Three of the 8 patients had MRSA infections that demonstrated a shift in the vancomycin MIC to 2 by broth microdilution antimicrobial susceptibility testing while on therapy. Six patients were switched to daptomycin due to persistent bacteremia on vancomycin despite vancomycin trough levels of 15-20 µg/ml. Dap-

tomycin was not used in 2 patients presumably due to pulmonary involvement with either septic emboli or empyema. The change to telavancin occurred in 2 of the 6 patients receiving daptomycin when they experienced fevers concerning for drug-induced fever. The remaining patients were switched to telavancin for persistent bacteremia on vancomycin or daptomycin.

Several patients had intermittent bacteremia. Patients with documented IE had valvular vegetation seen on either transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE). Of the two patients with possible IE, one refused a TEE, and the other had a negative TEE. Three patients had concomitant vertebral osteomyelitis, one had psoas abscess, one had multiple septic joint infections, one had multiple skin abscesses, and another had a testicular abscess.

The decision to change to telavancin was driven by persistently positive blood cultures. Of note, for 6 of the 8 patients, the last blood cultures taken before telavancin was started were negative indicating recent clearance of the bacteremia. For the remaining 2 patients with positive MRSA blood cultures at the time of telavancin was started, both had sterilization of their blood cultures on telavancin therapy. One had negative cultures after 24 hours on telavancin. The other did not have repeat blood cultures collected until the third day of telavancin therapy.

No direct adverse effects of telavancin were documented. One patient experienced persistent fevers on telavancin despite resolution of bacteremia. This was the patient who refused a TEE to rule out IE and a potential complication of IE that might have explained the fever. He completed a full course of therapy for bacteremia and the fevers resolved. No new or worsening cases of renal failure were documented.

One of the 8 patients died while receiving telavancin. This patient suffered a cardiac arrest 2 days into telavancin therapy, on post-op day 2 from an aortic valve replacement and mitral valve repair for endocarditis with aortic root abscess and AV block. A second patient with documented aortic valve endocarditis was readmitted 8 days after discharge with pleural effusions and shortness of breath and died a few days later. It is unclear if this patient had been discharged with vancomycin or telavancin due to issues with ensuring access to telavancin in the long term care facility. When he was readmitted, his blood cultures were positive for MRSA. It is unclear if this represents clinical failure of vancomycin or telavancin.

Discussion:

In this retrospective case series, 8 patients received telavancin for treatment of MRSA bacteremia with or without IE, with prior microbiologic failure with vancomycin and/or daptomycin. As described above, due to the delay in the reporting of positive blood culture results, some of the patients had cultures clear on previous antibiotic therapy. However, most of them had prolonged bacteremia (7-16 days) on vancomycin and/or daptomycin.

Three of the patients had MRSA strains with a vancomycin MIC of 2, and 2 of the 3 patients had initial MICs to vancomycin that increased on therapy. The daptomycin MICs did not change significantly during therapy, but 4/8 patients exhibited continued bacteremia on daptomycin. An older study demonstrated a trend toward increased vancomycin clearance in IVDAs, although the

results were not statistically significant (Rybak et al. 1990). We have noted this phenomenon among IVDAs at our institution, with the need to give very high doses of vancomycin to achieve adequate serum level, which may increase the likelihood of toxicity. Telavancin carries a boxed warning stating that it can cause increased mortality in patients with pre-existing creatinine clearance (<50 ml/min) and can also cause new onset of worsening renal impairment. Worsening of existing renal impairment in our series was not observed.

In conclusion, this retrospective case series presents patients successfully treated with telavancin for complicated MRSA bacteremia infection including IE. This agent may be a useful tool in our fight against refractory MRSA bacteremia. While randomized controlled trials are the best way to study efficacy and toxicity, our series indicates that telavancin, while not FDA approved for endocarditis or complicated bacteremia, may be a worthwhile agent for salvage therapy when none of the FDA approved agents can be given or if they have failed to clear the infection.

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