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Successful Treatment of Prosthetic Joint Infection due to Vancomycin-resistant Enterococci with Tedizolid

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Abstract

Few antibiotic options exist for the management of infections due to vancomycin-resistant enterococci (VRE). We describe a case involving the safe and successful use of tedizolid, a new oxazolidinone, to treat VRE prosthetic joint infection.

Keywords

tedizolid; vancomycin-resistant enterococci; prosthetic joint infection

Vancomycin-resistant enterococci (VRE) have become increasingly frequent and challenging to treat. From 2003 to 2006, hospitalizations with VRE-related infection more than doubled, and as of 2009, VRE was the second most common cause of nosocomial infection in the U.S. [1, 2]. Furthermore, vancomycin resistance is present in up to 79 percent of *Enterococcus faecium* isolates [2].

Currently, one antibiotic, linezolid, an oxazolidinone, is approved by the U.S. Food and Drug Administration (FDA) for the treatment of infections due to VRE. Tedizolid, a next-generation oxazolidinone currently FDA-approved for acute bacterial skin and skin-structure infections, including those caused by *Enterococcus faecalis* but not *E. faecium* exhibits broad-spectrum activity against the majority of Gram-positive organisms, including VRE. Here, we present a case describing the novel, unlabeled use of tedizolid for a prolonged period (4 weeks) to treat a prosthetic joint infection (PJI) due to vancomycin-resistant *E. faecium*.

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CASE REPORT

A 51-year-old woman with a history of total right hip arthroplasty (THA) 17 months prior, complicated by recurrent PJI, presented with rhabdomyolysis after 2 weeks of treatment with daptomycin. Following her initial right THA, she had developed recurrent PJI due to a number of different organisms, requiring explantation of her prosthesis, 5 subsequent surgical incision and debridements, and multiple courses of antimicrobial therapy (Figure 1). Intraoperative cultures were positive for several pathogens: vancomycin-sensitive *E. faecalis*, coagulase-negative staphylococci, and *Pseudomonas aeruginosa*. However, intraoperative cultures collected from the patient's acetabulum and hip fascia during the most recent debridement yielded coagulase-negative staphylococci and vancomycin-resistant *E. faecium*, susceptible to daptomycin, linezolid, doxycycline, and quinupristin-dalfopristin (Table 1). Gram stain performed on these specimens did not reveal any polymorphonuclear leukocytes or microorganisms. Daptomycin was started 2 weeks prior to her presentation with a significant reduction in the pain and swelling of her affected hip. Unfortunately, she developed severe pain in both forearms and was diagnosed with rhabdomyolysis with a peak serum creatine kinase level > 28,000 units/L. Daptomycin was promptly discontinued and her rhabdomyolysis resolved.

In light of the susceptibility of the isolated *E. faecium* to linezolid, the patient was started on tedizolid 200 mg PO once daily. Her past psychiatric history was notable for major depression and anxiety, for which she was prescribed venlafaxine, amitriptyline, and doxepin. These were discontinued as a precaution upon discussion with her primary care physician prior to receiving tedizolid. The patient was continued on ciprofloxacin to treat the previously isolated *P. aeruginosa.* In total, the patient was treated with tedizolid in an inpatient setting for 28 days with significant clinical improvement in her PJI and a reduction in her serum C-reactive protein from 35.1 mg/L (before the start of daptomycin) to 4.1 mg/L at discharge. At no point did she manifest symptoms of serotonin syndrome or treatment-related thrombocytopenia. At four-month follow-up after discontinuation of tedizolid, she had no clinical signs of relapse of VRE PJI and has not received chronic suppressive antibiotic therapy. A joint aspiration was not performed after completion of treatment with tedizolid.

DISCUSSION

This case demonstrates the successful use of tedizolid to treat vancomycin-resistant *E. faecium* PJI. Although enterococci are responsible for only a small fraction (about 3–10%) of PJIs, the emergence of VRE presents a significant therapeutic challenge [3, 4]. Tedizolid is an attractive candidate for the treatment of VRE, surpassing linezolid for several reasons. *In vitro*, tedizolid may be a more potent drug, with several-fold lower minimum inhibitory concentrations (MIC) against VRE than linezolid [5]. Furthermore, tedizolid appears to retain activity against linezolid- and daptomycin-resistant enterococci, displaying MIC values on average 4- to 8-fold lower compared to linezolid [6]. Commerical methods for antimicrobial susceptibility testing of tedizolid are not routinely available, and there are no interpretive criteria for defining susceptibility in *E. faecium.* In this case, susceptibility of the VRE to tedizolid was inferred from the isolate's susceptibility to linezolid, as linezolid

susceptibility has been shown to be highly predictive of tedizolid susceptibility. In one study, 99.8% of enterococcal isolates that were susceptible to linezolid were also susceptible to tedizolid [7]. Finally, tedizolid may be better tolerated than linezolid, with several studies suggesting a significantly lower risk of serotonin syndrome and thrombocytopenia compared to linezolid [8–10].

Little is known regarding the use or efficacy of tedizolid in the treatment of PJI. No studies have investigated the penetration of tedizolid into synovial fluid or bone to date. The effectiveness of tedizolid against staphylococci isolated from prosthetic joint infections was assayed in one study [11]. All isolates of *Staphylococcus aureus* and *Staphylococcus epidermidis* were susceptible to tedizolid in a planktonic state, but against isolates in a biofilm state, MICs for tedizolid were ~1–2 dilutions higher. This pattern was similarly observed for vancomycin as well. Yet, the clinical improvement of our patient may be evidence that tedizolid reaches adequate killing concentrations in bone and synovium.

Specific guidelines do not exist for the optimal management of PJI caused by VRE, although daptomycin and linezolid are often used and are recommended for the treatment of PJI due to penicillin-resistant enterococci [12]. Tedizolid should be considered as an alternative agent to treat VRE PJI in the setting of antibiotic resistance, medication intolerance, or potential drug-drug interactions.

CONCLUSION

Our case describes the novel, successful, and unlabeled use of tedizolid in the treatment of PJI secondary to vancomycin-resistant *E. faecium*. The safe, extended duration (4 weeks) of treatment suggests that tedizolid can be used for managing infections requiring prolonged therapy such as PJI, with the potential for less hematological toxicity and risk of interaction with serotonergic agents compared to linezolid. Further research is warranted to better characterize the clinical efficacy of tedizolid against VRE in PJI and other osteoarticular infections.

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References

1. Ramsey AM, Zilberberg MD. Secular trends of hospitalization with vancomycin-resistant enterococcus infection in the United States, 2000–2006. Infect Control Hosp Epidemiol. 2009; 30:184–6. [PubMed: 19125679]

2. Sievert DM, Ricks P, Edwards JR, et al. National Healthcare Safety Network (NHSN) Team and Participating NHSN Facilities. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. Infect Control Hosp Epidemiol. 2013; 34:1–14. [PubMed: 23221186]
3. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. 2004; 351:1645–54. [PubMed: 15483283]
4. Sia IG, Berbari EF, Karchmer AW. Prosthetic joint infections. Infect Dis Clin North Am. 2005; 19:885–914. [PubMed: 16297738]
5. Schaadt R, Sweeney D, Shinabarger D, Zurenko G. In vitro activity of TR-700, the active ingredient of the antibacterial prodrug TR-701, a novel oxazolidinone antibacterial agent. Antimicrob Agents Chemother. 2009; 53:3236–9. [PubMed: 19528279]
6. Barber KE, Smith JR, Raut A, Rybak MJ. Evaluation of tedizolid against Staphylococcus aureus and enterococci with reduced susceptibility to vancomycin, daptomycin or linezolid. J Antimicrob Chemother. 2016; 71:152–5. [PubMed: 26476277]
7. Zurenko G, Bien P, Bensaci M, Patel H, Thorne G. Use of linezolid susceptibility test results as a surrogate for the susceptibility of Gram-positive pathogens to tedizolid, a novel oxazolidinone. Ann Clin Microbiol Antimicrob. 2014; 13:46–52. [PubMed: 25238753]
8. Flanagan S, Bartizal K, Minassian SL, Fang E, Prokocimer P. In vitro, in vivo, and clinical studies of tedizolid to assess the potential for peripheral or central monoamine oxidase interactions. Antimicrob Agents Chemother. 2013; 7:3060–6.
9. Shorr AF, Lodise TP, Corey GR, et al. Analysis of the phase 3 ESTABLISH trials of tedizolid versus linezolid in acute bacterial skin and skin structure infections. Antimicrob Agents Chemother. 2015; 59:864–71. [PubMed: 25421472]
10. Prokocimer, P., Bien, P., Munoz, KA., Aster, R. Hematological effects of TR-701, linezolid and placebo administered for 21 days in healthy subjects. Proceedings of the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; Washington, DC, USA. 25–28 October 2008;
11. Schmidt-Malan SM, Greenwood Quaintance KE, Karau MJ, Patel R. In vitro activity of tedizolid against staphylococci isolated from prosthetic joint infections. Diagn Microbiol Infect Dis. 2016; 85:77–9. [PubMed: 26906190]
12. Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013; 56:1–25. [PubMed: 23230301]

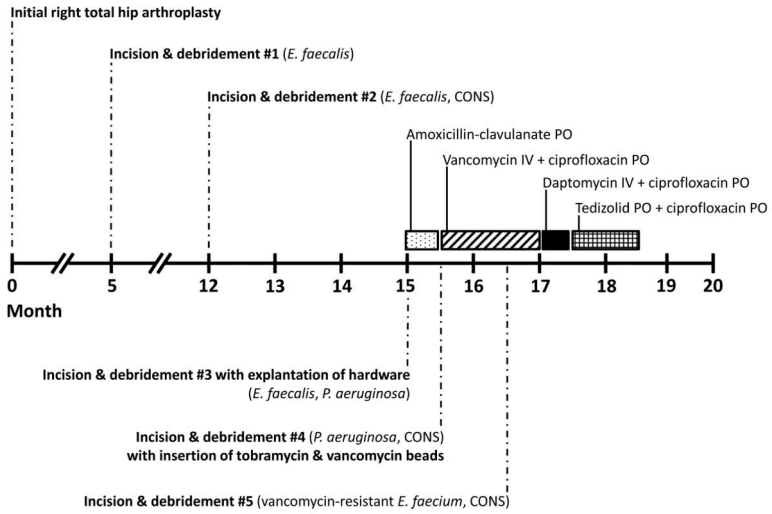

Figure 1.

Case timeline, including surgeries, operative cultures, and antimicrobial therapy. CONS: coagulase-negative staphylococci

Table 1

Antimicrobial susceptibility of *Enterococcus faecium* isolated from intraoperative culture, as determined by disc diffusion testing (Kirby-Bauer method) following Clinical and Laboratory Standards Institute (CLSI) guidelines.

Antimicrobial	Result
Ampicillin	Resistant
Daptomycin	Susceptible
Doxycycline	Susceptible
Linezolid	Susceptible
Quinupristin-Dalfopristin	Susceptible
Vancomycin	Resistant