AAC Journals.ASM.org

Daptomycin-Nonsusceptible Vancomycin-Intermediate *Staphylococcus aureus* Vertebral Osteomyelitis Cases Complicated by Bacteremia Treated with High-Dose Daptomycin and Trimethoprim-Sulfamethoxazole

Lisa M. Avery,[a,b] Molly E. Steed,[c]* Ashley E. Woodruff,[a] Muhammad Hasan,[b] and Michael J. Rybak[c,d]

Wegman's School of Pharmacy, St. John Fisher College, Rochester, New York, USA[a]; St. Joseph's Hospital Health Center, Syracuse, New York, USA[b]; Anti-Infective Research Laboratory, Eugene Applebaum College of Pharmacy & Health Sciences[c] and School of Medicine,[d] Wayne State University, Detroit, Michigan, USA

We report two cases of daptomycin (DAP)-nonsusceptible (DNS) vancomycin-intermediate *Staphylococcus aureus* (VISA) vertebral osteomyelitis cases complicated by bacteremia treated with high-dose daptomycin and trimethoprim-sulfamethoxazole. Both patients responded rapidly and favorably to this combination. The clinical isolates from the two patients were tested *post hoc* in an *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) model to confirm the bactericidal activity and enhancement of daptomycin and trimethoprim-sulfamethoxazole. The combination of high-dose daptomycin and trimethoprim-sulfamethoxazole should be explored further for the treatment of DNS VISA strains.

Treatment of *Staphylococcus aureus* infections displaying decreased susceptibility to both vancomycin and daptomycin (DAP) is challenging. Agents that retain activity are generally bacteriostatic, making the clearance of bacteria in deep-seated infections like osteomyelitis difficult, or they have concerning adverse effect profiles. This is especially true if appropriate surgical intervention and debridement cannot be performed. The following two cases illustrate the use of a novel bactericidal combination of high-dose daptomycin and trimethoprim-sulfamethoxazole (SXT) for the treatment of daptomycin-nonsusceptible (DNS) vancomycin-intermediate *Staphylococcus aureus* (VISA) vertebral osteomyelitis.

(A portion of this work was presented as a poster presentation at the 51st Interscience Conference on Antimicrobial Agents and Chemotherapy [ICAAC], Chicago, IL, 2011.)

In February 2010, an 80-year-old male with a history of methicillin-resistant *Staphylococcus aureus* (MRSA) infections presented as an outpatient to his primary care physician with nausea, vomiting, and hypotension. Blood cultures were obtained, and 48 h later, the Gram stain was positive for Gram-positive cocci. The patient was admitted to the hospital and treated with vancomycin intravenously (i.v.) after 3 days of oral linezolid therapy as an outpatient. Results from both a three-phase nuclear bone scan and magnetic resonance imaging (MRI) of the spine were consistent with T9 and T10 vertebra osteomyelitis, discitis, and paravertebral phlegmon. Surgical debridement was not considered due to the location of the infection. A transesophageal echocardiogram was negative for endocarditis.

On hospital day 3 (day 3 in the hospital), vancomycin was discontinued, and 650 mg of quinupristin-dalfopristin (7.5 mg/kg of body weight) i.v. every 8 h was initiated based on culture results. The outpatient blood cultures had two distinct *S. aureus* isolates: *S. aureus* H9749-1 (vancomycin MIC of 16 μg/ml and daptomycin MIC of 2 μg/ml) and isolate two (vancomycin MIC of 2 μg/ml and daptomycin MIC of 0.5 μg/ml). Both isolates were susceptible to SXT (Table 1). On hospital day 5, the patient was switched to daptomycin (10 mg/kg/day) plus SXT i.v. (8 mg/kg/day of the trimethoprim [TMP] component) given every 8 h based on *in vitro* evidence of bactericidal activity against a DNS heterogeneous VISA (hVISA) strain (23). Repeat blood cultures taken on hospital admission were negative. On hospital day 11, the patient was transitioned to oral therapy, two double-strength (DS) SXT tablets twice daily while continuing daptomycin 10 mg/kg/day. On day 16 of hospitalization, his serum creatinine (SCr) rose to 2.0 mg/dl, and he complained of intolerable nausea and vomiting. Daptomycin (10 mg/kg/day) was continued, but the SXT dose was decreased to one DS SXT tablet twice daily. Twenty-four days later, his serum creatinine returned to baseline and he was put back on two DS SXT tablets twice daily with daptomycin (10 mg/kg/day). The patient tolerated the daptomycin-SXT combination therapy for 2 months when his creatinine phosphokinase (CPK) increased to 1,280 IU/liter without symptoms of myopathy. Daptomycin was discontinued, and the CPK level returned to baseline (17 IU/liter). He completed 6 months of SXT suppression therapy and was deemed a clinical cure.

In June 2010, a 65-year-old female with a history of recurrent MRSA leg wounds with bacteremia was admitted to the hospital with intractable back pain. A MRI of the spine showed T6 to T7 vertebral enhancement, suspicious for vertebral osteomyelitis, with no evidence of an abscess. Surgical debridement was not performed due to the location of the infection. On hospital day three, the patient was switched from empirical vancomycin i.v. to daptomycin at 6 mg/kg per day when the Gram stain method was positive for Gram-positive cocci. Two separate peripheral blood cultures grew *S. aureus* isolate F31774 with a vancomycin MIC of

Received 21 May 2012 Returned for modification 25 June 2012
Accepted 1 August 2012
Published ahead of print 6 August 2012
Address correspondence to Michael J. Rybak, m.rybak@wayne.edu.
* Present address: Molly E. Steed, University of Kansas School of Pharmacy, Lawrence, Kansas, USA.

doi:10.1128/AAC.01046-12

TABLE 1 Vitek 2 MICs for VISA isolates

Antimicrobial agent(s)	MIC[a] (mg/liter) of antimicrobial agent for:		
	Case 1		
	Isolate 1 (*S. aureus* H9749-1)	Isolate 2	Case 2, isolate 1 (*S. aureus* F31774)
Quinupristin-dalfopristin	0.5	1	N/A
Daptomycin	2 [2–4]	0.5 [0.25]	4 [4]
Gentamicin	≤0.5	≤0.5	≤0.5
Linezolid	2	4	2
Telavancin	(0.38)[b]	(1)[b]	0.5
SXT	<0.5/9.5 [0.03/0.6]	<0.5/9.5 [0.03/0.6]	<0.5/9.5 [0.03/0.6]
Rifampin	≥32	≥32	≤0.5 [<0.06]
Tigecycline	0.25	0.5	≤0.12
Clindamycin	≥8	≥8	≥8
Oxacillin	≥4	≥4	≥4
Vancomycin	16 [8–16]	2	2 (3)[b] [4]

[a] MIC confirmed by broth microdilution at the Anti-Infective Research Laboratory shown in brackets. N/A, not available (no quinupristin-dalfopristin disks were available due to back order). For trimethoprim-sulfamethoxazole (SXT), the value for trimethoprim is shown before the slash and the value for sulfamethoxazole is shown after the slash.
[b] MIC by Etest.

2 μg/ml by automated susceptibility testing (Vitek 2), 3 μg/ml when repeated by Etest, and confirmed VISA with a MIC of 4 μg/ml by the New York State reference laboratory. The daptomycin MIC was 4 μg/ml (Table 1). On day six, the daptomycin dose was increased to 10 mg/kg/day, and SXT i.v. (8 mg/kg/day of the TMP component) given every 8 h was added after repeat blood cultures remained positive. The blood cultures were negative 48 h later. The patient tolerated the high-dose SXT given i.v. in combination with daptomycin therapy for 7 days (hospital day 12), while repeat blood cultures remained negative (day 10), until her SCr increased to 2.6 mg/dl (from a baseline of 1.2 mg/dl) with potassium of 6.0 mmol/liter, prompting the discontinuation of SXT and replacement with oral rifampin (300 mg) given three times daily. Her CPK increased to 164 IU/liter on day 11 of daptomycin (baseline CPK 33 IU/liter) without myopathy. On day 15 of hospitalization, the patient experienced an increase in dyspnea, and chest computed tomography (CT) revealed numerous pulmonary nodules thought to be septic emboli from a presumed tricuspid valve endocarditis; however, a transesophageal echocardiogram could not be performed. Blood cultures remained negative. Linezolid (600 mg given i.v.) every 12 h was added to provide greater pulmonary coverage. Despite aggressive therapy, the patient died on day 19 of hospitalization.

All *Staphylococcus* isolates were tested using an automated testing system, Vitek 2 (bioMérieux), vancomycin Etest strips (bioMérieux), and sent to the New York State Health Department for confirmation. *Post hoc*, isolates were then sent to the Wayne State University Anti-Infective Research Laboratory for confirmation of MIC by broth microdilution (BMD) via Clinical and Laboratory Standards Institute (CLSI) guidelines and synergy testing via an *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) model (6).

One-compartment *in vitro* PK/PD model. A 48-h *in vitro* PK/PD one-compartment model as previously described was utilized to simulate human pharmacokinetic parameters (22, 24, 25). Pharmacodynamic samples from each model were collected over 48 h and plated for bacterial enumeration. Bactericidal activity (99.9% kill) was defined as a ≥3 $\log_{10}$ CFU/ml reduction in colony count from the initial inoculum. Enhancement of activity was defined as an increase in killing of ≥2 $\log_{10}$ CFU/ml by a combination of antimicrobial agents versus the most active single agent alone. Reductions in colony counts were determined over a 48-h period and compared for the different regimens. Changes in CFU/ml at 0 to 48 h were compared by one-way analysis of variance with Tukey's Post-Hoc test. A P value of ≤ 0.05 was considered significant. All statistical analyses were performed using IBM SPSS statistical software (release 19.0; SPSS, Inc., Chicago, IL).

MIC values measured by Vitek 2 and BMD for isolates placed in the PK/PD models can be seen in Table 1. The activity of daptomycin, vancomycin, SXT, and daptomycin plus SXT against *S. aureus* strain H9749-1 in the *in vitro* PK/PD model are displayed in Fig. 1A. Vancomycin and SXT were bacteriostatic, while daptomycin displayed sustained bactericidal activity from 8 to 48 h. The combination of daptomycin plus SXT was rapidly bactericidal (8 h), reached the limit of detection (1 $\log_{10}$ CFU/ml) at 24 h, and was significantly better than either agent alone (24 to 48 h) ($P \leq 0.004$).

The activity of daptomycin, vancomycin, SXT, rifampin, daptomycin plus SXT, and daptomycin plus rifampin against *S. aureus* strain F31774 in the *in vitro* PK/PD model can be seen in Fig. 1B. Bacteriostatic activity was observed for vancomycin, daptomycin, SXT, and rifampin. Daptomycin plus SXT displayed sustained bactericidal activity (32 to 48 h) and was significantly better than either agent alone at 48 h ($P < 0.001$). Daptomycin plus rifampin were bactericidal (24 to 48 h) and significantly better than either agent alone (48 h) ($P < 0.001$) and was better than daptomycin plus SXT only at 24 h ($P = 0.04$).

There are limited case reports of VISA bone and joint infections. Successful outcomes have been reported with linezolid monotherapy, linezolid with fusidic acid, linezolid with rifampin, quinupristin-dalfopristin, and a combination of vancomycin, nafcillin, and gentamicin (11–13, 17, 18). SXT and daptomycin have concentration-dependent bactericidal activity against VISA/hVISA strains and also have clinical data to support their use in the treatment of osteomyelitis (5, 7, 9, 18, 23, 26). Multiple studies have evaluated the safety of high-dose daptomycin and found the incidence of symptomatic myopathy and CPK elevation to be comparable to that of standard doses (4, 8, 10, 14, 15, 20). Dapto-

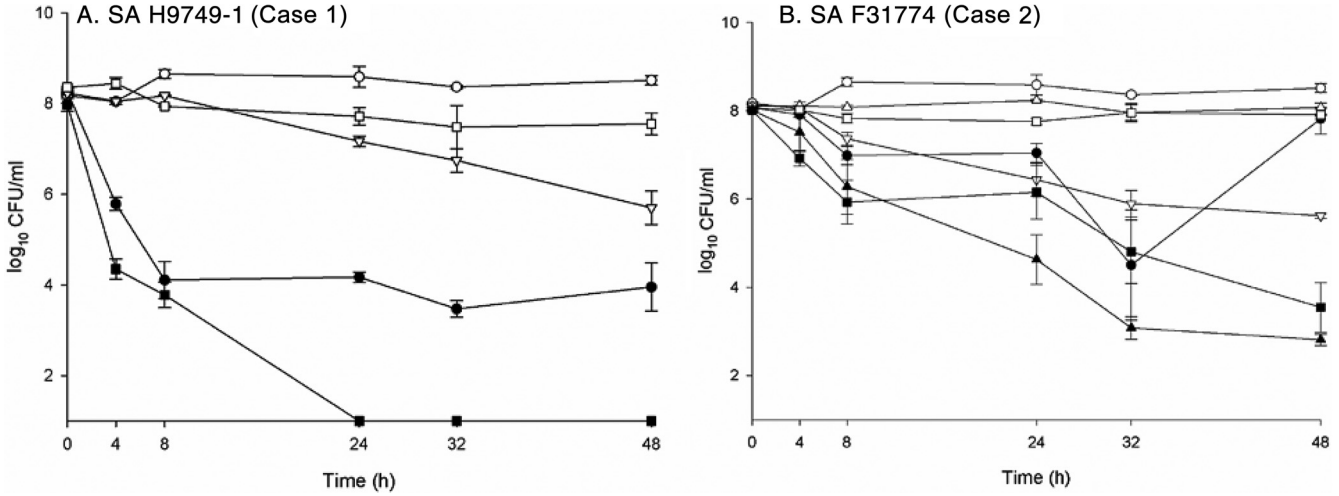

FIG 1 Activity of tested antimicrobial agents in a one-compartment *in vitro* pharmacokinetic/pharmacodynamic model. The antimicrobial agents were tested against *S. aureus* (SA) H9749-1 and *S. aureus* F31774. Symbols: ○, no drug (growth control); ●, daptomycin (10 mg/kg) every 24 h (maximum concentration of the free, unbound fraction of drug in serum [fC_{max}] of 13.17 mg/liter and half-life [$t_{1/2}$] of 8 h); ▽, vancomycin (1 g) every 12 h (q12h) (fC_{max} of 15 mg/liter and $t_{1/2}$ of 6 h); △, rifampin (300 mg) every 24 h (fC_{max} of 0.8 mg/liter and $t_{1/2}$ of 3 h); □, trimethoprim-sulfamethoxazole (160/800 mg) every 12 h (fC_{max} of 1.3 and 30 mg/liter, respectively, and $t_{1/2}$ of 10 h for each drug); ■, daptomycin plus trimethoprim-sulfamethoxazole; ▲, daptomycin plus rifampin.

mycin regimens up to 12 mg/kg/day have been studied in healthy patients and in patients with deep-seated VISA infections (2, 16). In each of our patient cases, CPK levels were elevated from normal baseline levels, but neither patient developed symptoms of myopathy despite these elevations. Adverse reactions of SXT include gastrointestinal symptoms, increased serum creatinine, and hyperkalemia (1, 3, 19). A rise in serum creatinine in both patients and hyperkalemia in the second patient led to reduction of the SXT dose in the first patient and cessation of SXT therapy in the second patient. Following cessation of SXT therapy, the second patient experienced a rapid clinical decline. It is important to note the *in vitro* data from the isolates from the two patients demonstrate bactericidal and enhancement of activity of daptomycin and SXT against DNS VISA at a lower dose of TMP (360 mg/day) than what was used initially in these cases. At this lower dose, an increase in creatinine is more likely due to competitive tubular secretion and not a change in the actual glomerular filtration rate, allowing patients to continue therapy and avoid switching to a less-effective regimen (3).

Although tested *post hoc*, the results from our *in vitro* PK/PD model correlated with the clinical outcomes. The first patient achieved osteomyelitis resolution, and the second patient cleared persistent bacteremia on daptomycin plus SXT. Concern has been raised regarding the efficacy of SXT in treating infections where high exogenous thymidine released from damaged host tissues may be present and antagonizing SXT activity (21). The clinical outcomes in our patients while on combination therapy with SXT were good, despite no surgical management to remove dead tissue, and correlated with the results of the *in vitro* model. Daptomycin appeared bactericidal when combined with rifampin in our model; however, this did not correlate with the second patient's clinical course and may represent an area for further research. High-dose daptomycin combined with SXT may be a viable option for patients with DNS VISA infections.

ACKNOWLEDGMENTS

M.J.R. has received grant support, consulted for, or provided lectures for Astellas, Cubist, Forest, Clinical Therapeutics, Theravance, and Rib-X. L.M.A has served as an advisory board member (Forest) and provided lectures (Astellas) and owns stock (Merck). M.E.S., A.E.W., and M.H. have no potential conflicts of interest.

REFERENCES

1. **Alappan R, Perazella MA, Buller GK.** 1996. Hyperkalemia in hospitalized patients treated with trimethoprim-sulfamethoxazole. Ann. Intern. Med. **124**:316–320.
2. **Benvenuto M, Benziger DP, Yankelev S, Vigliani G.** 2006. Pharmacokinetics and tolerability of daptomycin at doses up to 12 milligrams per kilogram of body weight once daily in healthy volunteers. Antimicrob. Agents Chemother. **50**:3245–3249.
3. **Berglund F, Killander J, Pompeius R.** 1975. Effect of trimethoprim-sulfamethoxazole on the renal excretion of creatinine in man. J. Urol. **114**:802–808.
4. **Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL.** 2010. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. Clin. Infect. Dis. **50**:1568–1574.
5. **Burdette SD.** 2009. Daptomycin for methicillin-resistant Staphylococcus aureus infections of the spine. Spine J. **9**(6):e5–e8. doi:10.1016/j.spinee.2008.11.008.
6. **Clinical and Laboratory Standards Institute.** 2011. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically - ninth edition: approved standard M7-A9. Clinical and Laboratory Standards Institute, Wayne, PA.
7. **Close SJ, McBurney CR, Garvin CG, Chen DC, Martin SJ.** 2002. Trimethoprim-sulfamethoxazole activity and pharmacodynamics against glycopeptide-intermediate Staphylococcus aureus. Pharmacotherapy **22**:983–989.
8. **Cubist Pharmaceuticals Inc.** 2003. Cubicin package insert. Cubist Pharmaceuticals Inc, Lexington, MA.
9. **Falagas ME, Giannopoulou KP, Ntziora F, Papagelopoulos PJ.** 2007. Daptomycin for treatment of patients with bone and joint infections: a systematic review of the clinical evidence. Int. J. Antimicrob. Agents **30**:202–209.
10. **Figueroa DA, et al.** 2009. Safety of high-dose intravenous daptomycin

treatment: three-year cumulative experience in a clinical program. Clin. Infect. Dis. **49**:177–180.
11. **Fridkin SK.** 2001. Vancomycin-intermediate and -resistant Staphylococcus aureus: what the infectious disease specialist needs to know. Clin. Infect. Dis. **32**:108–115.
12. **Graber CJ, et al.** 2007. Intermediate vancomycin susceptibility in a community-associated MRSA clone. Emerg. Infect. Dis. **13**:491–493.
13. **Howden BP, et al.** 2004. Treatment outcomes for serious infections caused by methicillin-resistant Staphylococcus aureus with reduced vancomycin susceptibility. Clin. Infect. Dis. **38**:521–528.
14. **Katz DE, et al.** 2008. A pilot study of high-dose short duration daptomycin for the treatment of patients with complicated skin and skin structure infections caused by gram-positive bacteria. Int. J. Clin. Practice **62**:1455–1464.
15. **Kullar R, et al.** 2011. High-dose daptomycin for treatment of complicated gram-positive infections: a large, multicenter, retrospective study. Pharmacotherapy **31**:527–536.
16. **Lichterfeld M, Ferraro MJ, Davis BT.** 2010. High-dose daptomycin for the treatment of endocarditis caused by Staphylococcus aureus with intermediate susceptibility to glycopeptides. Int. J. Antimicrob. Agents **35**:96. doi:10.1016/j.ijantimicag.2009.08.019.
17. **Mariani PG, Sader HS, Jones RN.** 2006. Development of decreased susceptibility to daptomycin and vancomycin in a Staphylococcus aureus strain during prolonged therapy. J. Antimicrob. Chemother. **58**:481–483.
18. **Markowitz N, Quinn EL, Saravolatz LD.** 1992. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of Staphylococcus aureus infection. Ann. Intern. Med. **117**:390–398.
19. **Masters PA, O'Bryan TA, Zurlo J, Miller DQ, Joshi N.** 2003. Trimethoprim-sulfamethoxazole revisited. Arch. Intern. Med. **163**:402–410.
20. **Moise PA, Hershberger E, Amodio-Groton MI, Lamp KC.** 2009. Safety and clinical outcomes when utilizing high-dose (≥8 mg/kg) daptomycin therapy. Ann. Pharmacother. **43**:1211–1219.
21. **Proctor RA.** 2008. Role of folate antagonists in the treatment of methicillin-resistant Staphylococcus aureus infection. Clin. Infect. Dis. **46**:584–593.
22. **Steed ME, et al.** 2011. Characterizing vancomycin-resistant Enterococcus strains with various mechanisms of daptomycin resistance developed in an in vitro pharmacokinetic/pharmacodynamic model. Antimicrob. Agents Chemother. **55**:4748–4754.
23. **Steed ME, Vidaillac C, Rybak MJ.** 2010. Novel daptomycin combinations against daptomycin-nonsusceptible methicillin-resistant Staphylococcus aureus in an in vitro model of simulated endocardial vegetations. Antimicrob. Agents Chemother. **54**:5187–5192.
24. **Steed ME, Vidaillac C, Winterfield P, Biek D, Rybak MJ.** 2012. Evaluation of ceftaroline activity versus ceftriaxone against clinical isolates of Streptococcus pneumoniae with various susceptibilities to cephalosporins in an in vitro pharmacokinetic/pharmacodynamic model. Antimicrob. Agents Chemother. **56**:2691–2695.
25. **Vidaillac C, Parra-Ruiz J, Winterfield P, Rybak MJ.** 2011. In vitro pharmacokinetic/pharmacodynamic activity of NXL103 versus clindamycin and linezolid against clinical Staphylococcus aureus and Streptococcus pyogenes isolates. Int. J. Antimicrob. Agents **38**:301–306.
26. **Yeldandi V, Strodtman R, Lentino JR.** 1988. In-vitro and in-vivo studies of trimethoprim-sulphamethoxazole against multiple resistant Staphylococcus aureus. J. Antimicrob. Chemother. **22**:873–880.