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Comparative *In Vivo* Efficacies of Epithelial Lining Fluid Exposures of Tedizolid, Linezolid, and Vancomycin for Methicillin-Resistant *Staphylococcus aureus* in a Mouse Pneumonia Model

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The antibacterial efficacies of tedizolid phosphate (TZD), linezolid, and vancomycin regimens simulating human exposures at the infection site against methicillin-resistant *Staphylococcus aureus* (MRSA) were compared in an *in vivo* mouse pneumonia model. Immunocompetent BALB/c mice were orally inoculated with one of three strains of MRSA and subsequently administered 20 mg/kg TZD every 24 hours (q24h), 120 mg/kg linezolid q12h, or 25 mg/kg vancomycin q12h over 24 h. These regimens produced epithelial lining fluid exposures comparable to human exposures observed following intravenous regimens of 200 mg TZD q24h, 600 mg linezolid q12h, and 1 g vancomycin q12h. The differences in CFU after 24 h of treatment were compared between control and treatment groups. Vehicle-dosed control groups increased in bacterial density an average of 1.1 logs. All treatments reduced the bacterial density at 24 h with an average of 1.2, 1.6, and 0.1 logs for TZD, linezolid, and vancomycin, respectively. The efficacy of TZD versus linezolid regimens against the three MRSA isolates was not statistically different ($P > 0.05$), although both treatments were significantly different from controls. In contrast, the vancomycin regimen was significantly different from TZD against one MRSA isolate and from linezolid against all isolates. The vancomycin regimen was less protective than either the TZD or linezolid regimens, with overall survival of 61.1% versus 94.7% or 89.5%, respectively. At human simulated exposures to epithelial lining fluid, vancomycin resulted in minimal reductions in bacterial counts and higher mortality compared to those of either TZD or linezolid. TZD and linezolid showed similar efficacies in this MRSA pneumonia model.

Methicillin-resistant *Staphylococcus aureus* (MRSA), including community-associated (CA) and health care-associated (HA) strains, continue to dominate the infectious disease landscape. MRSA strains USA100, USA300, and USA400 are increasingly more resistant to antimicrobials and are spread over the United States and globally (3, 10, 13, 23, 27). As this species continues to adapt, the treatment of both CA-MRSA and HA-MRSA pneumonia has become more difficult (27, 33). Tedizolid phosphate (TZD; formerly torezolid phosphate) is a novel oxazolidinone antibiotic that is under investigation in phase III trials for acute bacterial skin and skin structure infections (ABSSSI) and has proven to be a powerful new agent against Gram-positive pathogens, including MRSA, *Streptococcus pneumonia*, and enterococci (2, 29). TZD is a prodrug antibiotic that is rapidly converted *in vivo* to the microbiologically active moiety tedizolid, also known as TR-700. Human pharmacokinetic studies of tedizolid showed improved pharmacokinetic results compared to those of linezolid and support a once-daily dose of 200 mg (25, 29). Additionally, tedizolid was shown to have *in vivo* efficacy in a pneumonia model of infection (26).

In this current study, the epithelial lining fluid (ELF) profile observed after the administration of 200 mg tedizolid every 24 hours (q24h) was studied in a mouse pneumonia infection model against both CA-MRSA and HA-MRSA strains. The determination of concentrations at the site of infection is now recommended for investigational drugs, and the approach of simulating human dosing exposures may show that such endeavors have additional significance (15, 24, 35). We have examined the efficacy of tedizolid compared to that of the sole FDA-approved oxazolidinone, linezolid (LZD), and the therapeutic standard, vancomycin (VAN), using ELF drug exposures in mice, which simulated those observed in humans.

MATERIALS AND METHODS

Bacterial strains. Three MRSA strains were used for these *in vivo* analyses. Two were CA-MRSA strains, 156 (USA300, Panton-Valentine leukocidin [PVL] negative, staphylococcal cassette chromosome *mec* type IV [SCC*mec* IV]) and 464 (PVL negative), and one was HA-MRSA, strain 56 (494 from Anti-Infective Research Laboratory, Detroit Receiving Hospital and University Health Center, Detroit, MI; USA100). Strains were maintained at −80°C and transferred onto agar medium for viability and to ensure uncontaminated growth before use in either *in vitro* or *in vivo* studies.

Antimicrobial agents. The analytical-grade TZD for *in vivo* studies and tedizolid for *in vitro* testing were both supplied by Albany Molecular Research Inc., Albany, NY. Linezolid was provided from Pfizer, Inc., Groton, CT. Vancomycin was acquired from Sigma-Aldrich Chemicals, St. Louis, IL. The antimicrobials were weighed and reconstituted in appropriate diluents to achieve the desired concentration each day of *in vivo* experimentation immediately prior to use. TZD was diluted in 0.025 M phosphate buffer, LZD in sterile water for injection, and VAN in normal saline. Both LZD and VAN solutions were stored under refrigeration pending the subsequent 12-h dose.

Received 22 December 2011 Returned for modification 18 January 2012 Accepted 11 February 2012
Published ahead of print 21 February 2012
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doi:10.1128/AAC.06427-11
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TABLE 1 MICs and characteristics of MRSA strains used during *in vivo* testing

Isolate[a]	Characteristics	Median MIC (range) (μg/ml)		
		Tedizolid	LZD	VAN
56	HA-MRSA, USA100	0.5	4 (4–8)	1
156	CA-MRSA, USA300	0.5	4 (2–4)	1
464	CA-MRSA, USA100	0.5	4 (2–4)	1 (0.5–1)

[a] Internal designation.

Antimicrobial susceptibility testing. The MRSA isolates were tested in accordance with Clinical and Laboratory Standards Institute by broth microdilution in triplicate for each compound (7). The median MICs and MIC ranges were reported.

Mouse infection model. Specific pathogen-free BALB/c female mice weighing approximately 20 g were obtained from Harlan Sprague Dawley, Inc. (Indianapolis, IN). Animals were maintained and used in accordance with National Research Council recommendations and allowed food and water *ad libitum*. This study was reviewed and approved by the Hartford Hospital Institutional Animal Care and Use Committee.

The immunocompetent *S. aureus* pneumonia model has been described elsewhere (9, 17, 20). In short, a volume of 0.05 ml of 10^9 CFU/ml MRSA bacterial suspension (in saline with 3% hog gastric mucin) was inoculated into each mouse. While the mice were anesthetized (2% isofluorane), the bacterial suspension was orally instilled and nares were blocked. The mouse aspirated suspension into the lungs while being held vertically for 60 s. Mice were randomized into vehicle or antimicrobial treatment groups consisting of six infected mice each and received the first administration of subcutaneous saline, intraperitoneal TZD, subcutaneous LZD, or subcutaneous VAN 3 h after inoculation. Mice were sacrificed and whole lung tissues were harvested from groups of animals prior to (0 h) and 24 h after commencement of dosing. The change in $\log_{10}$ CFU was calculated as the difference in the average number of CFU per group at 24 h minus the initial (0-h control) CFU level. Bacterial densities outside one standard deviation (SD) were excluded from the group average. The survival of the animals over the 24 h was monitored.

Determination of the ELF concentration profile. Single doses of each antimicrobial were administered to separate cohorts of six infected mice. Bronchoalveolar lavage fluid (BAL fluid) and blood (for urea only) was collected as described previously (17, 21) from groups of mice over the 12- to 24-h dosing intervals. TZD was administered via intraperitoneal injection at 6, 8.4, 18, and 20 mg/kg; LZD subcutaneously at 60, 120, and 180 mg/kg; and VAN subcutaneously at 20, 25, and 110 mg/kg. Cells in the BAL fluid were removed by centrifugation, and supernatant was stored at −80°C until analysis for antimicrobial agents. Blood samples for urea determination were separated by centrifugation and stored at −80°C.

Concentrations of tedizolid in BAL fluid were analyzed by matrix-validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) by Midwest Bioresearch, Skokie, IL, as previously reported (29). The upper and lower limits of quantification were 1,000 ng/ml and 10 ng/ml, respectively.

LZD was assayed by validated high-performance liquid chromatography (HPLC) procedures (37). Briefly trichloroacetic acid and an internal standard (4-nitroaniline) were added to the BAL fluid samples. After centrifugation, the aqueous layer was injected onto a C_{18} column with a pH 5 sodium acetate buffer-acetonitrile (80:20, vol/vol) with peaks monitored at 251 nm. The ratio of peak height to internal standard relative to the linear regression equation from prepared stock solutions was used to determine the sample concentration. Assay limits over 0.2 to 30 μg/ml were linear ($r^2 \geq 0.99$), with percent coefficient of variation between 1.4 to 4.5%.

VAN concentrations were assayed by high-pressure liquid chromatography. BAL fluid samples underwent centrifugation after the addition of the internal standard (caffeine) and acetonitrile. The aqueous phase was evaporated to dryness under nitrogen. Reconstitution was made with 200 μl of mobile phase consisting of phosphate buffer-acetonitrile at 89:11 (vol/vol). Samples were injected onto a C_{18} column (Spherisorb, 5 μm; Phenominex, Inc., Torrance, CA) and monitored at 198 nm. Linearity of the assay was well defined ($r^2 = 1.0$). The sample concentration was determined as described above for LZD; assay limits were 0.1 to 10 μg/ml with variability between 2.8 to 4.3%.

Each blood and BAL fluid sample was tested for urea concentration using a commercially available urea assay (TecoDiagnostics, Anaheim, CA). Linearity was highly consistent with correlation of ≥0.99 over the assay range of 0.1 to 2.0 mg/dl; variability was 0.2% to 2.9%. Accuracies of quality-control samples were between 93.1 and 98.3% recovery and 1.3% to 3.3% variance. The drug concentrations in ELF were calculated from the following formula: ELF concentration = BAL fluid concentration × (blood urea concentration/BAL fluid urea concentration) (21, 42). The area under the drug concentration-time curve (AUC) in ELF for all three regimens was calculated using the trapezoidal rule. The target AUC from 0 to 24 h (AUC_{0-24}) ELF exposures after administration of 200 mg TZD q24h, 600 mg LZD q12h, and 1 g VAN q12h were 109, 960, and 92 mg · h/liter, respectively (8, 16, 30, 38), in healthy adults.

Statistical comparison of antimicrobial efficacies. The differences between the average change in $\log_{10}$ CFU in lung from control and treatment groups at 24 h was evaluated using a one-way analysis of variance (ANOVA; SigmaStat version 2.03; SPSS, Inc., San Rafael, CA). A *P* value of <0.05 was considered significant.

RESULTS

MICs. The tedizolid, LZD, and VAN MIC values for each MRSA isolate are listed in Table 1. All isolates were susceptible to both LZD and VAN. Likewise, these isolates would be interpreted as susceptible with the proposed ≤2 μg/ml breakpoint for tedizolid and represent the MIC_{90} (2, 5). Tedizolid had 2- to 8-fold greater potency than VAN and LZD against these MRSA isolates.

Analysis of pharmacokinetic data to produce human simulated regimens of tedizolid, LZD, and VAN in ELF. The pharmacokinetic profile for each antimicrobial in mouse ELF is displayed in Fig. 1. The mouse concentration profiles for tedizolid, LZD, and VAN replicated the AUC_{0-24} exposures in humans and also demonstrated peak concentrations comparable to that observed in humans (8, 16, 30). The relevant ELF exposures (AUC_{0-24}) for tedizolid, LZD, and VAN are shown in Table 2.

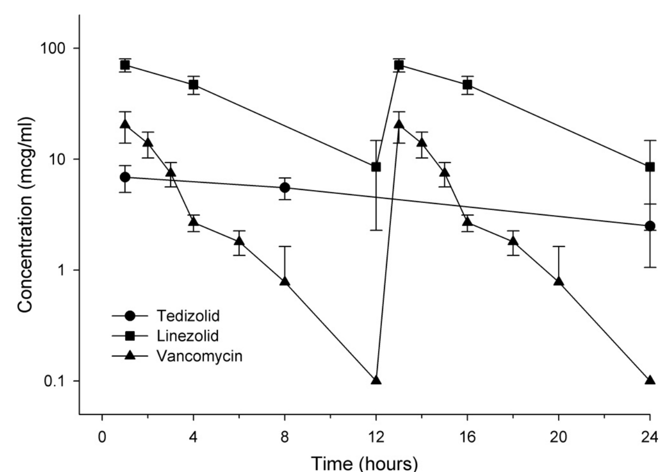

FIG 1 ELF concentration time course of 20 mg/kg tedizolid q24h (circle), 120 mg/kg LZD q12h (square), and 25 mg/kg VAN q12h (triangle) over 24 h in mice.

TABLE 2 Comparative ELF exposures of tedizolid, linezolid, and vancomycin in human and mouse pneumonia models

Compound	Human ELF AUC_{0-24}	Mouse ELF AUC_{0-24}	Mouse regimen
Tedizolid	109	111	20 mg/kg q24h
LZD	960	910	120 mg/kg q12h
VAN	92	104	25 mg/kg q12h

Comparative efficacy studies in the *in vivo* pneumonia model. Studies to evaluate the efficacies of the above-described dosages of TZD, LZD, and VAN as ELF exposures against the three MRSA strains were conducted in immunocompetent mice. The change in $\log_{10}$ CFU/ml for each treatment against each of the MRSA isolates is graphically displayed in Fig. 2. At the start of therapy, mice had between 7.28 to 7.54 $\log_{10}$ CFU in lung tissues for all MRSA isolates. After 24 h, bacterial densities in lung tissues from control groups contained 8.41 to 8.59 $\log_{10}$ CFU, an increase of approximately 1 log. Tedizolid diminished CFU loads by 0.76 to 1.4 logs at 24 h. Likewise, the LZD regimen lowered bacterial density ranging between 1.2 and 2.0 logs. No statistical differences were found between the tedizolid and LZD against any of the three MRSA isolates ($P > 0.05$); however, both regimens resulted in a statistically significant reduction in bacterial density compared with that of the vehicle-dose controls ($P \leq 0.005$). The VAN treatment was not nearly as efficacious; the bacterial density change averaged only slightly better than stasis, with an average decrease of 0.13 logs against the three MRSA isolates after 24 h. A statistical difference was found between the VAN regimens and control against two MRSA isolates (56 and 156; $P = 0.012$) but not the third, MRSA isolate 464 ($P = 0.142$). The variability around the average VAN CFU counts against *S. aureus* isolate 464 was large, possibly inhibiting detection of any divergence. Both tedizolid and LZD were more efficacious against MRSA isolate 56 versus VAN ($P = 0.016$ and 0.013, respectively). Additionally, the VAN regimen was statistically less efficacious than LZD against MRSA 156 ($P = 0.026$) and MRSA 464 ($P = 0.023$).

Average survival following each treatment regimen and in control groups was monitored. With the VAN treatment, an average of 39% of the mice perished before the end of the 24-h treatment interval for the three *S. aureus* isolates, a value similar to the 32% mortality noted in untreated controls. The TZD and LZD treatments were entirely protective against the MRSA isolates 56 and 464 and only one and two animals infected with *S. aureus* isolate 156 expired during TZD and LZD treatment, respectively.

DISCUSSION

Staphylococcus aureus is a frequently identified etiologic agent in bacterial pneumonia (13, 39, 40). As the incidence of methicillin-resistant *S. aureus* strains is increasing, the severity of infection and health care costs have increased (13, 23, 27, 33, 34). While vancomycin remains a frequently used treatment for pneumonia caused by MRSA, clinical failures in this setting have been increasingly recognized (12, 31, 32). As such, additional treatment options appear necessary as MRSA isolates with reduced VAN susceptibilities (MIC, 2 μg/ml) are becoming more prevalent and may contribute to poorer clinical outcomes (22, 32, 41). In addition to reductions in potency, the relatively low penetration (~50%) of vancomycin into ELF has also been suggested as a reason for the compound's diminished clinical efficacy (6, 22, 30, 35).

In a novel class of antimicrobial with which to treat MRSA pneumonia, LZD, an oxazolidinone, offers better human pharmacokinetics than VAN, and penetration of LZD into ELF is approximately 400% compared to that of blood (4, 8, 28). Moreover, unlike vancomycin, LZD does not require therapeutic monitoring to optimize drug exposures while minimizing its toxic potential. LZD is a commonly used alternative to VAN for the treatment of pneumonia due to *S. aureus*, including MRSA (19, 28, 39, 40). TZD, a next-generation oxazolidinone, has recently undergone clinical efficacy assessments for treatment of skin and soft-tissue infections, including MRSA (1, 11). Owing to its long half-life, excellent ELF penetration ratios, and potent *in vitro* activity, TZD is being considered a potential therapeutic agent for pneumonia caused by susceptible microorganisms, including MRSA (1, 16, 25, 26, 29).

The measurement of drug in the blood, while well established in the literature, may not always be indicative of concentrations at the site of infection, such as in central nervous system or respiratory infections. The concentration of drug at the site of infection must be assessed in order to better evaluate the antibacterial activity of a given antimicrobial and is a current requirement of the FDA (15, 24, 35). Many mouse studies have described the efficacy of antimicrobials based on the human simulated blood concentrations; however, few have simulated the *in vivo* exposure of humans at the site of infection (9, 18, 36).

In this study, the activities of TZD, LZD, and VAN were compared at the infection site at exposures in mice reproducing those found in human ELF. Our study also incorporated the effect of an intact immune system in mice, thus incorporating the proposed theory of increased granulocyte impact on bacterial kill as proposed for tedizolid (14).

The efficacy data from this study is consistent with that from another pneumonia study with tedizolid. In the dose-ranging

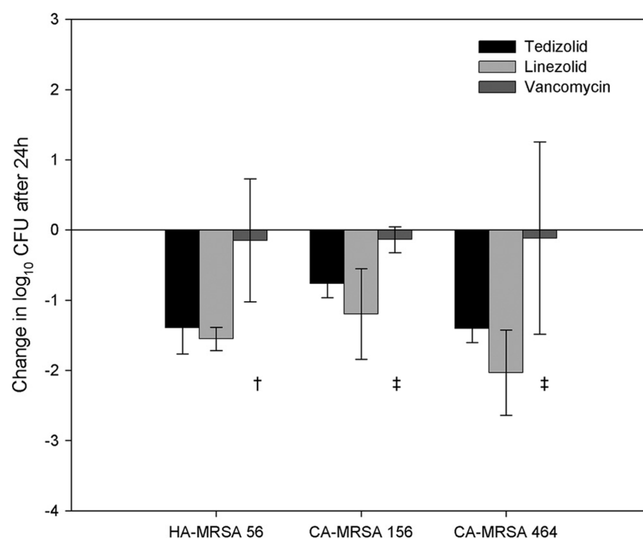

FIG 2 Changes in bacterial density after 24 h for tedizolid (black bar)-, LZD (light-gray bar)-, and VAN (dark-gray bar)-treated groups (bar level represents average change in $\log_{10}$ CFU of group from initial density; error bars, ±1 SD). †, significantly different from tedizolid and LZD, $P \leq 0.016$; ‡, significantly different from LZD, $P \leq 0.026$.

study by Pichereau et al., tedizolid demonstrated greater efficacy than LZD in a neutropenic murine pneumonia model (26). The TZD and LZD doses which produced a 1-log net decrease against MRSA were approximately 10 and 60 mg/kg, respectively, against MRSA. In our current study, the LZD regimen needed to simulate the human ELF exposure was 12-fold higher than that of the TZD; however, the *in vivo* efficacies of the two compounds were comparable. Although the doses needed to produce approximately a 1-log decrease in bacterial density differed between the studies, this was likely due to the varied host conditions (i.e., neutropenic versus immunocompetent) and the resultant differences in antimicrobial exposures among these models (17).

Our study revealed a previously unidentified aspect of treatment outcomes. While drug ELF exposures were consistent with that in humans, this short-term efficacy trial revealed not only minimal reductions in bacterial load with VAN but also that a larger percentage of the mice perished before the 24-h treatment was completed; only the vehicle-dosed controls fared worse over this period. Conversely, 95% and 89% survived during TZD and LZD treatment, respectively.

In summary, the efficacy of TZD, a novel oxazolidinone antibiotic, was compared with linezolid and vancomycin against strains of MRSA in an *in vivo* pneumonia model using dosing regimens that simulated human exposure at the site of infection. Both TZD and LZD were effective in this rigorous pneumonia model, while VAN showed minimal efficacy and higher mortality compared to those of either TZD or LZD. These data support the use of LZD and TZD for the treatment of pneumonia due to MRSA and support the continued development of TZD for this indication.

ACKNOWLEDGMENTS

This study was sponsored by a grant from Trius Therapeutics, San Diego, CA.

Thanks are extended to Michael J. Rybak for providing MRSA 56 (no. 494). We acknowledge the superior assistance of Deborah Santini, Lindsay Tuttle, Jennifer Hull, Henry Christensen, Mary Banevicius, Christina Sutherland, Mao Hagihara, and Seth Housman in the performance of this study.

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