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Comparative Efficacies of Human Simulated Exposures of Tedizolid and Linezolid against *Staphylococcus aureus* in the Murine Thigh Infection Model

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Tedizolid (formally torezolid) is an expanded-spectrum oxazolidinone with enhanced *in vitro* potency against Gram-positive pathogens, including methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA). The efficacies of human simulated exposures of tedizolid and linezolid against *S. aureus* in an immunocompetent mouse thigh model over 3 days were compared. Four strains of MRSA and one of MSSA with tedizolid and linezolid MICs ranging from 0.25 to 0.5 and from 2 to 4 μg/ml, respectively, were utilized. Tedizolid or linezolid was administered in a regimen simulating a human steady-state 24-h area under the free concentration-time curve of 200 mg every 24 h (Q24) or 600 mg Q12, respectively. Thighs were harvested after 4, 8, 12, 24, 36, 48, and 72 h, and efficacy was determined by the change in bacterial density. The mean bacterial density in control mice increased over the 3-day period. After 24 h of treatment, a reduction in bacterial density of ≥1 log CFU was observed for both the tedizolid and linezolid treatments. Antibacterial activity was enhanced for both agents with a reduction of ≥2.6 log CFU after 72 h of treatment. Any statistically significant differences ($P \leq 0.05$) in efficacy between the agents were transient and did not persist throughout the 72-h treatment period. The tedizolid and linezolid regimens demonstrated similar *in vivo* efficacies against the *S. aureus* isolates tested. Both agents were bacteriostatic at 24 h and bactericidal on the third day of treatment. These data support the clinical utility of tedizolid for skin and skin structure infections caused by *S. aureus*, as well as the bactericidal activity of the oxazolidinones after 3 days of treatment.

Acute bacterial skin and skin structure infections (ABSSSI) are frequently caused by Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) (35). While vancomycin is still considered the gold standard therapy for MRSA (29), treatment failures have been reported while the infecting pathogen is still susceptible to vancomycin (8, 10, 11, 24, 33). Moreover, studies have suggested a potential for vancomycin "MIC creep" or incremental increases in the MIC over time (22, 28, 34). While these increases have not been noted in national or global surveillance studies to date (13, 30), the reported clinical vancomycin failures, the advocacy for higher vancomycin exposures, and the need for more aggressive concentration monitoring highlight the need for alternative therapies targeting MRSA.

Tedizolid (TR-700, formerly torezolid), the active moiety of tedizolid phosphate is a novel expanded-spectrum oxazolidinone with activity against Gram-positive pathogens (16, 26), including MRSA. Much interest has emerged in comparing the *in vitro* and *in vivo* efficacies of TR-700 and the only other FDA approved oxazolidinone, linezolid (LZD), against clinically relevant pathogens. Against *S. aureus* and other Gram-positive pathogens, TR-700 has shown 4- to 16-fold greater *in vitro* activity than LZD and may have activity against LZD-resistant strains (3, 12, 15, 31, 32). Additionally, in a phase 2 study evaluating the safety and efficacy of TR-700 for the treatment of ABSSSI, the clinical cure rates were 96.6% and 96.8% for patients with *S. aureus* and MRSA infections, respectively (6). Our study was undertaken to compare the *in vivo* efficacies of human simulated exposures of TR-700 and LZD against *S. aureus* in the immunocompetent murine thigh infection model.

MATERIALS AND METHODS

Antimicrobial test agents. Analytical-grade tedizolid phosphate and LZD were used for the *in vivo* analyses. In the *in vitro* analyses, analytical-grade TR-700 and LZD were utilized. Immediately prior to each *in vivo* experiment, tedizolid phosphate and LZD were diluted in 0.025 M sodium phosphate dibasic solution and sterile water, respectively, to achieve the desired concentration. The solutions were stored under refrigeration and discarded 24 h after reconstitution.

Bacterial isolates. Five clinical isolates of *S. aureus* were utilized in this study. Four isolates were MRSA, including one community-acquired MRSA isolate and three hospital-associated MRSA isolates, of which one was also vancomycin resistant. The remaining isolate was methicillin-susceptible *S. aureus* (MSSA). MICs of both agents were determined by broth microdilution according to Clinical and Laboratory Standards Institute guidelines (5). Isolates were stored at −80°C in double-strength skim milk (Remel, Lenexa, KS), subcultured twice onto Trypticase soy agar with 5% sheep blood (Becton Dickinson and Co., Sparks, MD), and grown for 18 to 24 h at 35°C prior to use in experiments.

Immunocompetent thigh infection model. Specific-pathogen-free female ICR mice weighing approximately 22 g each were obtained from Harlan Sprague-Dawley, Inc. (Indianapolis, IN), and utilized throughout these experiments. This study was reviewed and approved by the Hartford Hospital Animal Care and Use Committee. Animals were maintained and

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used in accordance with National Research Council recommendations and were provided food and water *ad libitum*.

A suspension of each isolate was freshly prepared from the second subculture of each organism and diluted in normal saline to achieve a final inoculum of 10^8 CFU/ml. Each thigh was inoculated intramuscularly with 0.1 ml of inoculum 2 h prior to the initiation of antimicrobial therapy.

Pharmacokinetic studies and determination of dosing regimen. Single doses of tedizolid phosphate and LZD were administered to infected, immunocompetent mice to determine a regimen that simulated the human steady-state exposures of 200 mg of TR-700 orally every 24 h and 600 mg of LZD intravenously every 12 h. The target indices were 24-h areas under the free drug concentration-time curve (*f*AUCs) of 3 μg · h/ml (2, 9) and 137 μg · h/ml (4, 23, 27) for TR-700 and LZD, respectively. The murine protein binding values utilized for TR-700 and LZD were 85% (25) (data on file at Trius Pharmaceuticals, San Diego, CA) and 30% (1, 14), respectively. The *f*AUCs for both of the regimens were calculated by using the trapezoidal rule. Blood samples were collected via cardiac puncture from groups of six mice at three or four time points over a 12- to 24-h dosing interval. Plasma (TR-700) and serum (LZD) samples, as dictated by the analytical procedures, were separated and stored at −80°C until analysis. TR-700 concentrations were analyzed by Midwest Bioresearch (Skokie, IL) using a validated liquid chromatography-tandem mass spectrometry assay (26). LZD concentrations were analyzed at the Center for Anti-Infective Research and Development laboratory at Hartford Hospital with a modified validated high-performance liquid chromatography assay (36). The standard curve was extended from 20 to 30 μg/ml, and the extraction was modified from deproteinization with 200 ml of acetonitrile to deproteinization with 150 ml of 7.5% trichloroacetic acid with no drying step. The upper and lower limits of quantification of the TR-700 assay were 1,000 and 10 ng/ml, respectively. The upper and lower limits of quantification of the LZD assay were 30 and 0.2 μg/ml, respectively. The intraday percentage coefficients of variation (CV) for the LZD quality control samples of 0.5 and 20 μg/ml were 4.89 and 3.15%, respectively, and the respective interday CV were 3.25 and 2.37%.

***In vivo* efficacy as assessed by bacterial density.** Five clinical *S. aureus* isolates were utilized in the immunocompetent thigh infection model to assess the efficacies of humanized exposure regimens of TR-700 and LZD. Two hours after inoculation, groups of three mice were administered the human simulated regimen of TR-700 as a 0.2-ml intraperitoneal injection and LZD as a 0.3-ml subcutaneous injection over a 72-h treatment period. Control mice were administered normal saline at the same time, in the same volume, and by the same route as the most frequent regimen. Groups of three untreated control mice were euthanized by CO_2 exposure, followed by cervical dislocation just prior to the initiation of therapy (0 h). Groups of TR-700-treated, LZD-treated, and control mice were sacrificed at 4, 8, 12, 24, 36, 48, and 72 h. Following sacrifice, both rear thighs were removed and homogenized individually in 5 ml of normal saline. Serial dilutions of thigh homogenate were subcultured onto Trypticase soy agar with 5% sheep blood for determination of bacterial density. Efficacy, defined as a change in bacterial density, was calculated as the difference in the $\log_{10}$ CFU/ml between the treated and control mice at the respective time points. A comparison of the efficacies of TR-700 and LZD against each isolate at each time point was made by using the Student *t* test. A *P* value of <0.05 was defined *a priori* as statistically significant.

RESULTS

Bacterial isolates. The phenotypic profiles of the five *S. aureus* isolates evaluated in this study are listed in Table 1. The TR-700 and LZD MICs for the isolates ranged from 0.25 to 0.5 and from 2 to 4 μg/ml, respectively.

Pharmacokinetic determination. In this study, we were able to define dosing regimens for both TR-700 and LZD to attain humanized 24-h *f*AUCs. In this model, we achieved exposures that simulated human regimens of TR-700 with a *f*AUC from time zero to 24 h ($fAUC_{0\text{-}24}$) of 2.99 μg · h/ml and LZD with a $fAUC_{0\text{-}24}$ of 144 μg · h/ml.

TABLE 1 Phenotypic profiles of the *S. aureus* test isolates used in this study for TR-700 and LZD

S. aureus isolate	Characteristics[a]	MIC (range) in μg/ml	
		TR-700	LZD
152	HA MRSA	0.5	4 (2–4)
156	CA MRSA	0.5	4 (2–4)
426	HA MRSA	0.25	2
433	MSSA	0.5	4
456	HA MRSA-VRSA	0.25	2

[a] HA, hospital acquired; CA, community acquired; VRSA, vancomycin-resistant *S. aureus*.

***In vivo* efficacy.** The mean bacterial density of control mice prior to the initiation of dosing was 6.89 $\log_{10}$ CFU, and the mean bacterial density increased to 7.34, 6.94, and 7.08 $\log_{10}$ CFU after 24, 48, and 72 h, respectively.

The TR-700 human simulated regimen produced 1.04 to 1.80, 2.13 to 2.68, and 2.68 to 3.72 $\log_{10}$ CFU reductions from the 0-h control at 24, 48, and 72 h, respectively, against all of the isolates in the immunocompetent thigh infection model (Fig. 1A to E). Similarly, reductions of 1.36 to 2.02, 2.19 to 3.11, and 2.64 to 3.76 $\log_{10}$ CFU were observed with the LZD human simulated regimen at the respective time points (Fig. 1A to E). While both agents would be defined as having bacteriostatic activity at 24 h, this activity was enhanced over time. By 72 h, both agents showed a considerable enhancement of overall killing that approximated or exceeded the bactericidal target of 3-log killing. Additionally, no statistically significant difference ($P > 0.05$) between treatments at 24 h was observed, with the exception *S. aureus* 152 ($P = 0.045$); however, there was no statistically significant difference between treatments prior to or after 24 h for this isolate. Also, one isolate each at both 48 h (*S. aureus* 433; $P = 0.002$) and 72 h (*S. aureus* 456; $P = 0.012$) showed a statistically significant difference between treatments in favor of LZD; however, this difference was not identified consistently throughout therapy. When considering the reduction in the bacterial density of the five *S. aureus* isolates as a whole, the two regimens produced similar reductions in CFU counts over the 72-h treatment period, regardless of the genotype or phenotype.

DISCUSSION

TR-700, the active moiety of the prodrug tedizolid phosphate, is an oxazolidinone with activity against Gram-positive pathogens, including MRSA. In addition to its spectrum of activity, TR-700 has been postulated to have a lower potential to induce resistance than the only FDA-approved oxazolidinone, LZD (16, 17, 18). In the present analysis, we evaluated the efficacies of human simulated exposures of TR-700 and LZD against a number of *S. aureus* strains, including MRSA, in an immunocompetent mouse thigh infection model. No sustained statistically significant difference in efficacy against the five *S. aureus* isolates tested was observed between the human simulated exposures of TR-700 once daily and LZD twice daily. Additionally, as treatment continued past the initial 24 h, enhanced antibacterial activity of both agents was observed, with an approximately 3-log overall bacterial count reduction over the 72-h treatment period.

Similar to LZD efficacy, the pharmacodynamic target associated with TR-700 efficacy is the AUC/MIC ratio (19). Previously,

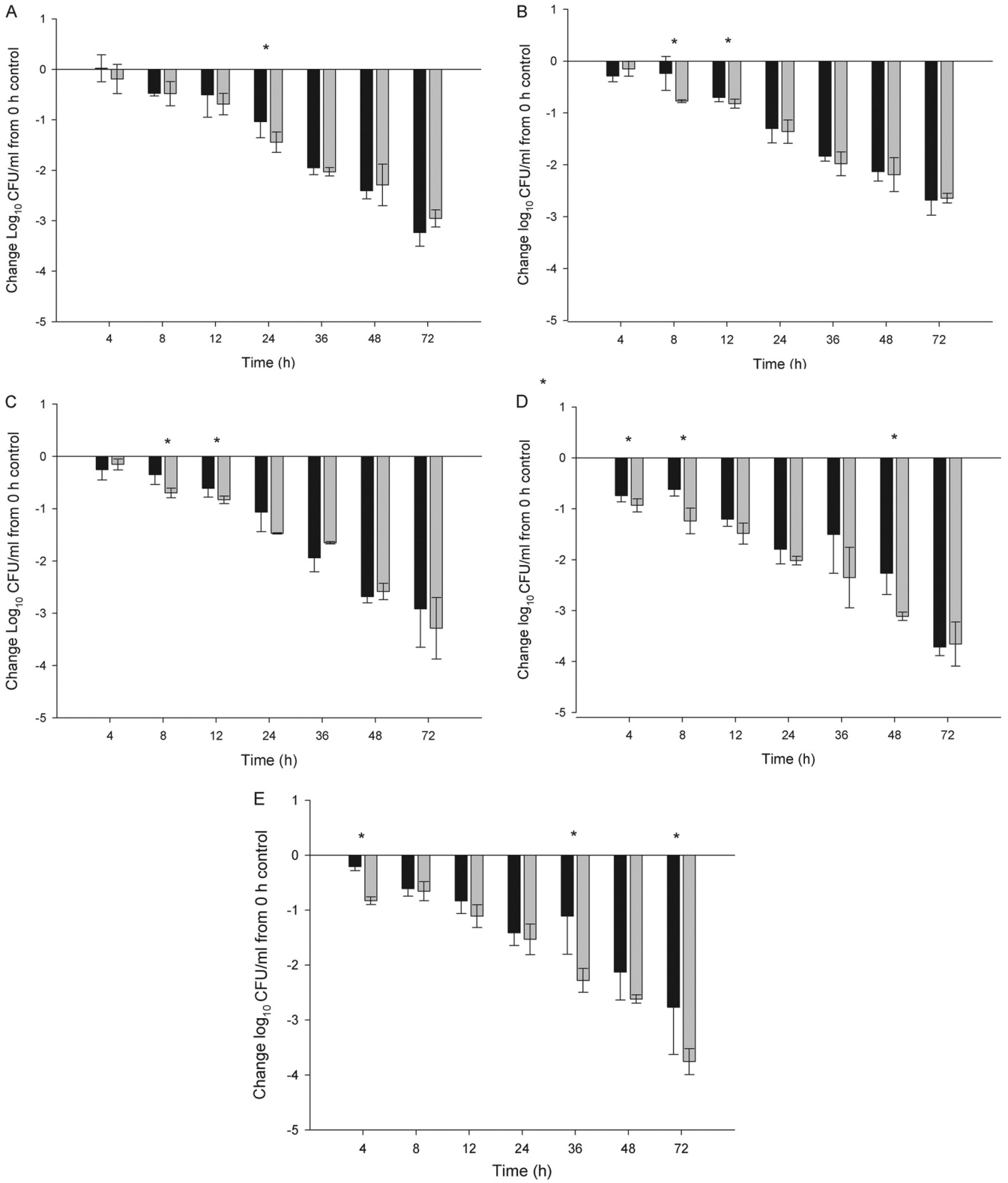

FIG 1 Log_{10} CFU counts of *S. aureus* 152 (A), 156 (B), 426 (C), 433 (D), and 456 (E) obtained with human simulated TR-700 (black bars) and LZD (gray bars) regimens at selected time points versus those of 0-h controls. Data are expressed as means ± standard deviations for three mice per group. An asterisk signifies a statistically significant difference between treatment groups.

it was noted that a lower AUC/MIC ratio is required for efficacy in immunocompetent mice than in neutropenic mice (7, 20). In the current study, using immunocompetent animals, the human simulated regimen of TR-700 achieved mean total drug AUC_{0-24}/MIC ratios of 79.7 and 39.8 for the isolates with TR-700 MICs of 0.25 and 0.5 μg/ml, respectively. For LZD, the pharmacodynamic index associated with efficacy is an AUC_{0-24}/MIC ratio of ≥83 (1, 21, 27) and our human simulated LZD regimen attained mean AUC_{0-24}/MIC ratios of 102.9 and 51.4 for those isolates with LZD MICs of 2 and 4 μg/ml, respectively. While having isolates with higher MICs of both agents would have helped identify the *in vivo* therapeutic breakpoint, the TR-700 MIC_{90} for *S. aureus* is 0.5 μg/ml while the LZD MIC_{90} is 4 μg/ml; thus, the isolates in the present study represent the upper end of the MIC distribution that would be encountered clinically (31).

In a phase 2 clinical trial using TR-700 in patients with ABSSSI, *S. aureus* was the most common pathogen, with TR-700 baseline MICs ranging from 0.12 to 0.5 μg/ml (26). For those with *S. aureus* identified at the baseline, clinical cure rates were >96% and pathogen eradication occurred between 88.9 and 100%, depending on the dose of TR-700 (doses ranged from 200 to 400 mg daily). These data, in conjunction with our murine data, support the continued development of TR-700 for the treatment of complicated skin and skin structure infections. The exposure of TR-700 and its reductions of CFU counts noted herein provide pharmacodynamic support for the clinical efficacy observed with this compound. Moreover, the cumulative bactericidal activity that TR-700 displayed over 72 h in this model provides additional pharmacodynamic evidence of its day 3 efficacy (i.e., cessation of lesion spread and resolution of fever), as observed in clinical trials of ABSSSI (6).

TR-700 is a novel expanded-spectrum oxazolidinone with *in vitro* potency against *S. aureus*, including MRSA, and has shown positive clinical outcomes in a setting of ABSSSI. In the immunocompetent murine thigh model, human simulated exposures of TR-700 and LZD resulted in similar efficacies against both methicillin-susceptible and -resistant *S. aureus*. Furthermore, the antibacterial activities of both agents were enhanced as therapy continued out to 72 h. A human simulated TR-700 dosage of 200 mg once daily resulted in efficacy against these *S. aureus* isolates with MICs up to and including 0.5 μg/ml. These data support the clinical utility and further development of TR-700 for use against *S. aureus* in the treatment of ABSSSI.

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