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Comparative Pharmacodynamics of the New Oxazolidinone Tedizolid Phosphate and Linezolid in a Neutropenic Murine *Staphylococcus aureus* Pneumonia Model

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Tedizolid phosphate (TR-701) is a novel oxazolidinone prodrug (converted to the active form tedizolid [TR-700]) with potent *Staphylococcus aureus* activity. The current studies characterized and compared the *in vivo* pharmacokinetic/pharmacodynamic (PD) characteristics of TR-701/TR-700 and linezolid against methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) in the neutropenic murine pneumonia model. The pharmacokinetic properties of both drugs were linear over a dose range of 0.625 to 40 mg/kg of body weight. Protein binding was 30% for linezolid and 85% for TR-700. Mice were infected with one of 11 isolates of *S. aureus*, including MSSA and community- and hospital-acquired MRSA strains. Each drug was administered by oral-gastric gavage every 12 h (q12h). The dosing regimens ranged from 1.25 to 80 mg/kg/12 h for linezolid and 0.625 to 160 mg/kg/12 h for TR-701. At the start of therapy, mice had 6.24 ± 0.40 $\log_{10}$ CFU/lungs, which increased to 7.92 ± 1.02 $\log_{10}$ CFU/lungs in untreated animals over a 24-h period. A sigmoid maximum-effect (E_{max}) model was used to determine the antimicrobial exposure associated with net stasis (static dose [SD]) and 1-log-unit reduction in organism relative to the burden at the start of therapy. The static dose pharmacodynamic targets for linezolid and TR-700 were nearly identical, at a free drug (non-protein-bound) area under the concentration-time curve over 24 h in the steady state divided by the MIC (AUC/MIC ratio) of 19 and 20, respectively. The 1-log-unit kill endpoints were also similar, at 46.1 for linezolid and 34.6 for TR-700. The exposure targets were also comparable for both MSSA and MRSA isolates. These dosing goals support further clinical trial examination of TR-701 in MSSA and MRSA pneumonia.

Staphylococcus aureus has become a leading cause of community- and hospital-acquired pneumonia. Furthermore, infection with community- and health care-acquired strains of methicillin-resistant *S. aureus* (MRSA) is increasingly common and limits antimicrobial options (13, 25, 29, 31). Tedizolid phosphate (TR-701) is a novel oxazolidinone prodrug. The active moiety, tedizolid (TR-700), exhibits potent activity against Gram-positive bacteria, including MRSA (48). The goals of our studies were to identify the pharmacodynamic (PD) target (AUC/MIC ratio) for TR-700 against methicillin-susceptible *S. aureus* (MSSA) and MRSA strains in a neutropenic murine pneumonia model and compare the PD targets of TR-700 to that of the only FDA-approved oxazolidinone antibiotic, linezolid.

MATERIALS AND METHODS

Bacteria, media, and antibiotics. Eleven isolates of *S. aureus* were utilized for these experiments. The strains included four MSSA strains (ATCC 6538P, ATCC 25923, ATCC 29213, and ATCC Smith), one hospital-acquired MRSA strain (ATCC 33591), and six community-acquired MRSA strains (MW2, R2527, 04-045, 04-154, 05-051, and UW 307109). Organisms were grown, subcultured, and quantified in Mueller-Hinton broth (Difco Laboratories, Detroit, MI) and Mueller-Hinton agar (Difco Laboratories, Detroit, MI). Linezolid was obtained from the University of Wisconsin pharmacy. Tedizolid (TR-700) and tedizolid phosphate (TR-701) were supplied by the manufacturer (Trius Therapeutics, San Diego, CA). Prior to *in vivo* treatment studies, TR-701 was dissolved in sterile water at the appropriate drug concentrations. TR-700 was dissolved in sterile dimethyl sulfoxide (DMSO) and diluted with medium to the appropriate concentration for *in vitro* susceptibility testing.

***In vitro* susceptibility studies.** The MICs of linezolid and TR-700 were determined three times in duplicate using Clinical and Laboratory Standards Institute (CLSI) microdilution methods M07-A8 (15). The duplicates were identical, and the final results were reported as the median value of the three MIC tests (see Table 1).

Murine infection model. All animal studies were approved by the Animal Research Committees of the University of Wisconsin and William S. Middleton Memorial VA Hospital. Six-week-old, specific-pathogen-free, female ICR/Swiss mice weighing between 24 and 27 g (Harlan Sprague-Dawley, Indianapolis, IN) were used for all studies. Three mice were utilized for each treatment and control group. Mice were rendered neutropenic (absolute neutrophil count of $<100/mm^3$) by injecting cyclophosphamide (Mead Johnson Pharmaceuticals, Evansville, IN) intraperitoneally 4 days (150 mg/kg of body weight) and 1 day (100 mg/kg) prior to experimental infection. Previous studies have shown that this regimen produces persistent neutropenia in this animal model for 5 days (3). Broth cultures of freshly plated bacteria were grown to logarithmic phase. The inoculum for each organism was diluted to a 0.3 absorbance at 580 nm. Viable plate count confirmation of the inoculum ranged from 10^6 to 10^7 CFU/ml. Animals were anesthetized by isoflurane inhalation. The mice were held upright, and 50 μl of the inoculum was administered to the nares and inhaled into the lung. Treatment commenced 2 h after challenge, at which time mice had 6.24 ± 0.40 $\log_{10}$ CFU/lungs.

Drug pharmacokinetics. Single-dose plasma pharmacokinetic (PK) studies were performed in infected mice given oral doses of linezolid (0.625, 2.5, 10, and 40 mg/kg) or TR-701 (0.625, 2.5, 10, and 40 mg/kg). Blood samples were obtained from groups of three mice at 0.25, 0.5, 1, 3,

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TABLE 1 *In vitro* activity of linezolid and TR-700 against select *S. aureus* isolates

Organism	MIC (mg/liter)[a]			
	Linezolid	TR-700	Methicillin	Lineage
MSSA				
ATCC 25923	2	0.06	0.25	
ATCC 29213	2	0.25	0.125	
ATCC 6538P		0.125	0.5	
ATCC Smith		0.5	0.125	
MRSA				
04-045	2	0.125	>16	
04-154	2	0.25	>16	
MW2	2	0.5	>16	USA400
307109		0.25	>16	
ATCC 33591		0.25	>16	USA200
R2527		0.125	>16	USA300
05-051		0.25	>16	

[a] The MICs are reported as the median values of three MIC tests.

6, 9, 12, and 24 h. The concentrations of compounds were analyzed by a validated liquid chromatography-tandem mass spectrometry (LC-MS-MS) by Midwest Bioresearch, Skokie, IL, as previously described (43). The assay lower limit of quantitation was 1 ng/ml, and the coefficient of variation ranged from 1 to 7%. A noncompartmental model was used for PK analyses. PK parameters, including elimination half-life and concentration at time zero (C_0), were calculated via nonlinear least-squares techniques. The area under the concentration-time curve (AUC) was calculated by the trapezoidal rule. For treatment doses in which no kinetics were determined, the PK index was estimated by linear extrapolation for higher and lower dose levels and interpolation for dose levels within the dose range studied. Protein binding was previously determined by the sponsor, Trius Pharmaceuticals (85%).

Treatment protocols. Two hours after pulmonary challenge, mice were treated with either linezolid or TR-701. Linezolid was administered by oral gavage (OG) every 12 h over a dose range of 1.25 to 80 mg/kg. TR-701 was administered by OG every 12 h over a dose range of 0.625 to 160 mg/kg. Groups of three mice were utilized for each dose administered, 0-h and 24-h untreated controls. After 24 h of treatment the mice were

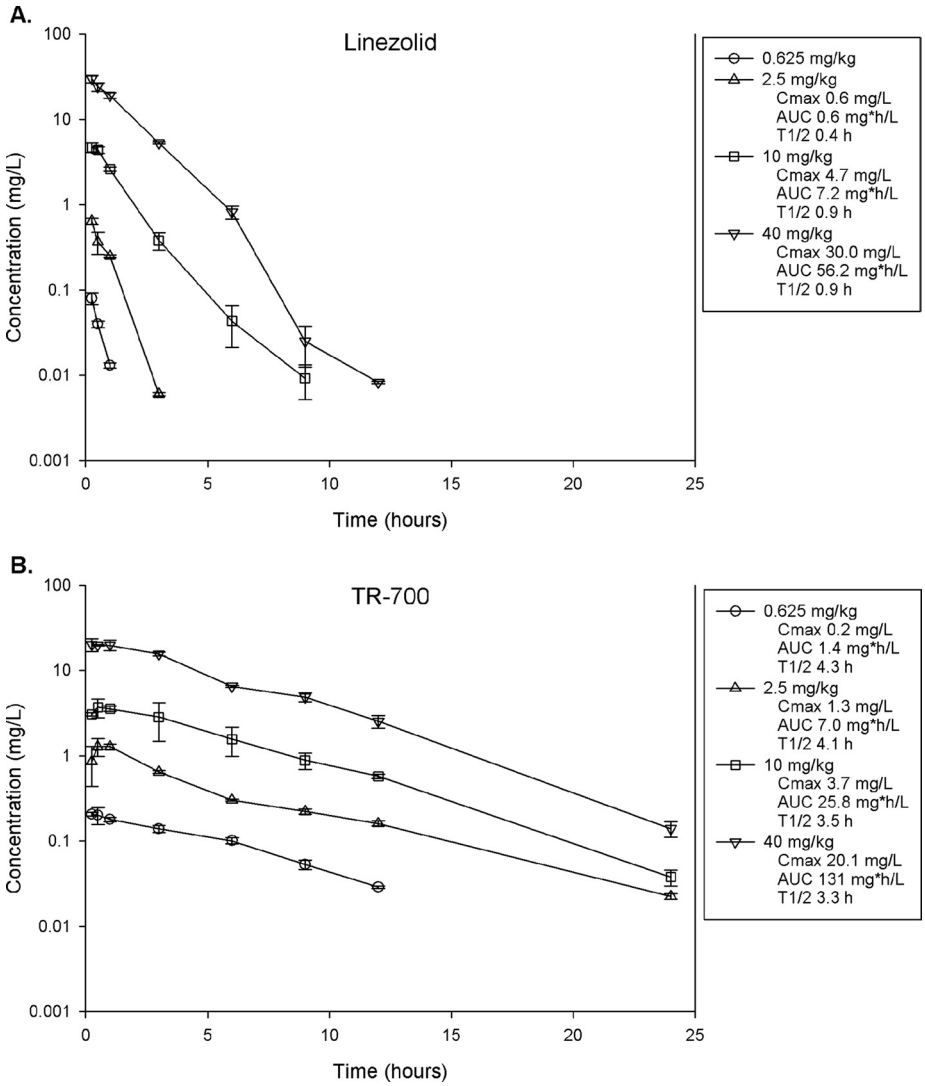

FIG 1 Concentrations for linezolid (A) and TR-700 (B) in plasma after administration of single oral doses of 0.625, 2.5, 10, and 40 mg/kg in neutropenic infected mice. Each symbol represents the geometric mean ± standard deviation (error bar) of the levels measured in three mice. Cmax, peak level in plasma; AUC, plasma $AUC_{0-\infty}$; T1/2, plasma elimination half-life (in hours). PK parameters were not determined for the lowest dose of linezolid, as there were too few data points to estimate these parameters.

euthanized by carbon dioxide asphyxiation. Untreated control mice were assessed at time of treatment initiation. Following euthanasia, the lungs were harvested using sterile technique, homogenized, diluted, plated, and incubated, and viable plate counts were assessed as previously described (18). Data are expressed as the mean change in $\log_{10}$ CFU/lungs for three mice per treatment group compared to the organism burden at the start of therapy.

Data analysis. The results were analyzed using a sigmoid E_{max} model: $\log_{10}$ SD = $\{\log_{10}[E/(E_{max} - E)]/N\} + \log ED_{50}$, where SD is the static dose or dose level necessary to maintain organism burden the same as at the start of treatment, E is the control growth, or in this case the log change in CFU/ml lung homogenate in untreated controls after 24 h, E_{max} is the maximum effect, ED_{50} is the dose required to achieve 50% of E_{max}, and N is the slope of the dose-response curve. The indices E_{max}, ED_{50}, and N were calculated for each drug and strain using nonlinear least-squares regression. The dose needed to achieve net stasis (SD) and 1-log-unit kill was determined using the formula for each drug against each strain tested. The area under the concentration-time curve over 24 h in the steady state divided by the MIC (AUC/MIC ratio) has been shown in previous studies to be the pharmacodynamic (PD) parameter predictive of treatment efficacy for oxazolidinones (8, 35). Therefore, the total drug AUC/MIC (tAUC/MIC ratio) and free drug (non-protein-bound) AUC/MIC (fAUC/MIC ratio) for each drug-organism combination was also determined. The coefficient of determination (R^2) was used to estimate the variance that could be due to regression with the drug exposure index. Analysis of variance (ANOVA) was used to determine whether the differences in PD target needed for stasis and killing were significant between linezolid and TR-700. The Mann-Whitney U test was used to compare TR-700 PD targets for MSSA and MRSA strain groups.

RESULTS

***In vitro* susceptibility testing.** The MICs of linezolid and tedizolid (TR-700) are listed in Table 1. The MICs for linezolid were the same for the five organisms tested, whereas the MICs for TR-700 varied by 8-fold (0.06 to 0.5 μg/ml). *In vitro* potency was 4- to 32-fold higher for TR-700. Methicillin potency did not influence the linezolid or TR-700 MICs.

Pharmacokinetics. The time course plasma levels of linezolid and TR-700 in infected neutropenic mice after oral administration of 0.625, 2.5, 10, and 40 mg/kg are shown in Fig. 1. PK parameters, including elimination half-life, maximum plasma drug concentration (C_{max}), and area under the drug-concentration curve from 0 h to infinity ($AUC_{0-\infty}$) are also shown; however, these were not determined for the lowest linezolid dose (0.625 mg/kg), as there were too few data points to accurately calculate the parameters. The plasma pharmacokinetics of both drugs were linear over the dose range (R^2 of >99% based upon linear regression of AUC). The elimination half-life of linezolid ranged from 0.4 to 0.9 h. The C_{max} increased from 0.6 to 30.0 mg/liter over the dose range, and the AUC ranged from 0.6 to 56.2 mg · h/liter. The elimination half-life of TR-700 ranged from 3.3 to 4.3 h. The C_{max} increased from 0.2 to 20.1 mg/liter over the dose range, and the AUC ranged from 1.4 to 131 mg · h/liter. Protein binding values were previously reported for linezolid at 30% (51). The binding value for TR-700 was based upon prior studies performed by the sponsor (85%).

Dose response, 24-h static dose, 1-log-unit kill determination. The dose-response curves following treatment with escalating doses of linezolid and tedizolid phosphate (TR-701) against 5 and 11 *S. aureus* isolates, respectively, are shown in Fig. 2. At the start of therapy, mice had 6.24 ± 0.40 $\log_{10}$ CFU/lung. The organisms grew to 7.92 ± 1.02 $\log_{10}$ CFU/lung in untreated control mice

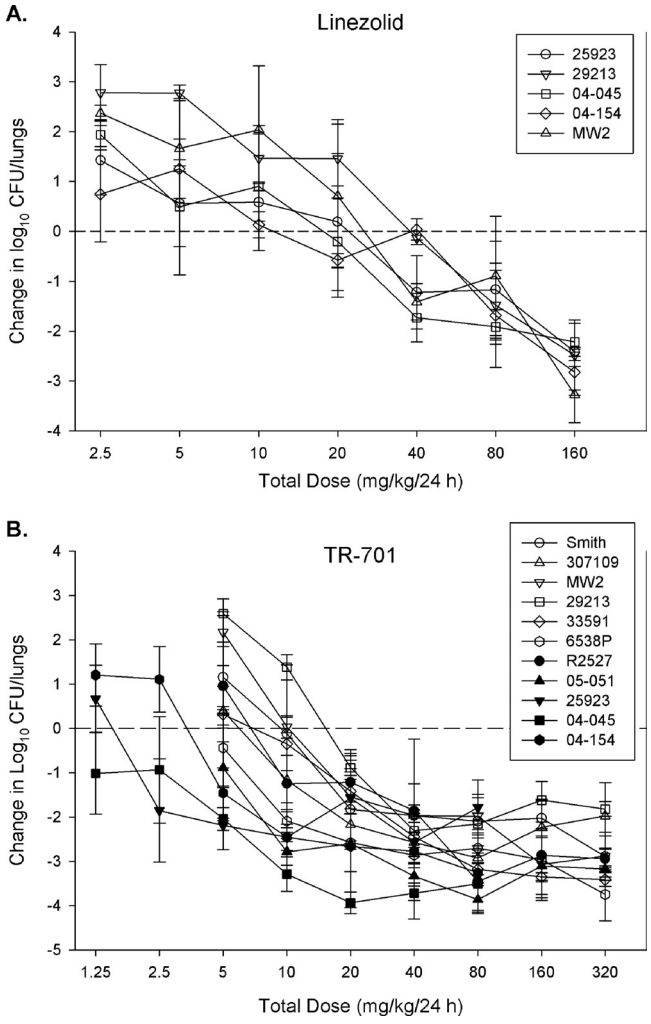

FIG 2 Dose-response relationships for linezolid (A) and TR-701 (B). Mice received one of a series of 2-fold increasing doses of linezolid or TR-701 every 12 h over a 24-hour treatment period. Each symbol represents the mean organism burden in the lungs of three mice. The error bars represent the standard deviations. The dashed horizontal line represents the organism burden at the start of therapy. Symbols below the line represent organism reduction compared to the start of therapy. Symbols above the line represent organism growth.

over 24 h. The maximal reductions of burden in *S. aureus*-infected mice treated with linezolid and TR-701 were 3.27 ± 0.56 $\log_{10}$ CFU/lung and 3.93 ± 0.24 $\log_{10}$ CFU/lung, respectively. The dose-response curves for linezolid were nearly identical, as were the *in vitro* MICs. The MIC variation for TR-700 did appear to impact the dose-response relationship. Higher TR-701 doses were needed for similar effects against organisms with higher MICs compared to those with lower MICs. Tables 2 and 3 show the 24-h total dose required to achieve a static effect and 1-log-unit kill for linezolid and TR-701 against each *S. aureus* isolate. The mean plasma 24-h tAUC/MIC ratios associated with a static endpoint were 27.2 and 133 for linezolid and TR-700, respectively. However, when protein binding was considered, the mean plasma fAUC/MIC ratios for linezolid and TR-700 were similar at 19 and 20, respectively. The mean plasma 24-h fAUC/MIC associated with 1-log-unit kill reduction was roughly 2-fold higher than that

TABLE 2 *In vivo* activity of linezolid against select *S. aureus* isolates[a]

S. aureus isolate or parameter	MIC (mg/liter)	SD (mg/kg/24 h)	24-h SD tAUC/MIC	24-h SD fAUC/MIC	1-log-unit kill dose (mg/kg/24 h)	24-h 1-log-unit kill tAUC/MIC	24-h 1-log-unit kill fAUC/MIC
S. aureus isolates							
ATCC 25923	2	18.8	21.6	15.1	50.1	70.3	49.2
ATCC 29213	2	35.1	48.2	33.7	61.6	86.5	60.5
MW2	2	30.3	40.4	28.3	52.6	73.8	51.7
04-154	2	13.6	13	9.1	39.8	55.8	39
04-045	2	13.4	12.7	8.9	31.8	42.7	28.9
Mean	**2**	**22.2**	**27.2**	**19**	**47.2**	**65.8**	**46.1**
Median	**2**	**18.8**	**21.6**	**15.1**	**50.1**	**70.3**	**49.2**
SD	**0**	**9.9**	**16.3**	**11.4**	**11.6**	**16.9**	**11.9**

[a] SD, static dose; tAUC/MIC, total drug AUC/MIC; fAUC/MIC, free drug (non-protein-bound) AUC/MIC. The means, medians, and static doses are shown in boldface type.

needed for stasis (46.1 for linezolid and 34.6 for TR-700) and were not significantly different ($P = 0.334$). Additionally, the plasma 24-h fAUC/MIC associated with net stasis and 1-log-unit kill was not significantly different in MSSA and MRSA isolates ($P = 0.41$) for TR-700. The relationships between the AUC/MIC ratio and effect for linezolid and TR-700 are shown in Fig. 3. The exposure-response relationships were relatively strong based upon the coefficient of determination ($R^2 = 0.68$ for linezolid and $R^2 = 0.48$ for TR-700).

DISCUSSION

Antimicrobial pharmacokinetic-pharmacodynamic (PK/PD) studies are useful to identify the therapeutic potential of a drug through the integration of the PK properties, *in vitro* potency (MIC), and outcome. These approaches have proven useful in guiding design of effective drug regimens in humans and the development of susceptibility breakpoints (1, 2, 17, 21, 40, 41, 45). The emergence of antibiotic resistance has further elevated the relevance of these investigations to optimize treatment strategies. Drug resistance in Gram-positive organisms, especially *S. aureus*, has become epidemic worldwide and is linked to escalating morbidity and mortality (19, 20, 52, 54). Among the infections produced by this pathogen, health care- and ventilator-associated pneumonia is associated with the most dismal outcomes, and *S. aureus* is now recognized as the most commonly implicated organism (28, 50). Recent experimental and clinical investigations suggest the potential advantage of treatment with the oxazolidinone linezolid for this disease state due to potency against MRSA and penetration into the infection site relative to vancomycin and daptomycin (12, 16, 24, 30, 36, 38, 56–58). The present studies were designed to characterize the PK/PD relationships of a new oxazolidinone, TR-701, for treatment of these infections. We further compared these PD relationships to those from a concurrent study of linezolid.

Prior PK/PD study with oxazolidinones, including TR-701, has demonstrated potency against both MSSA and MRSA and the relevance of the AUC/MIC index (2, 22, 23, 27, 34, 35, 37, 44, 53, 55). For example, Louie et al. (35) performed a dose fractionation PK/PD evaluation of TR-701 against MRSA and MSSA using the murine thigh infection model. The total daily dose ranged from 0 to 100 mg/kg and was fractionated into every 24 h (q24h), q12h, and q6h dosing regimens. The dose-response curves were nearly identical for each dosing interval, suggesting that the amount of drug rather than the dosing frequency was most important for optimizing efficacy. Analysis of the dose fractionation data demonstrated that the AUC/MIC ratio was the driving PD index with the strongest regression fit ($R^2 = 0.98$).

While the index associated with therapeutic success has been

TABLE 3 *In vivo* activity of TR-701 or TR-700 against select *S. aureus* isolates[a]

S. aureus isolate or parameter	MIC (mg/liter)	TR-701 SD (mg/kg/24 h)	TR-700 24-h SD tAUC/MIC	TR-700 24-h SD fAUC/MIC	TR-701 1-log-unit kill dose (mg/kg/24 h)	TR-700 24-h 1-log-unit kill tAUC/MIC	TR-700 24-h 1-log-unit kill fAUC/MIC
S. aureus isolates							
ATCC Smith	0.5	9.1	86.8	13	14	148.3	22.2
UW 307109	0.25	6.4	124.6	18.7	9.5	181	27.3
MW2	0.5	11	108.1	16.2	15.9	173.2	26
ATCC 29213	0.25	14.3	303.7	45.5	20.3	461	69.2
ATCC 33591	0.25	7.5	144.2	21.6	15.3	331.1	49.7
ATCC 6538P	0.125	3.7	145.9	21.9	6.3	242.9	36.4
R2527	0.125	7.2	277.3	41.6	13.9	588.2	88.2
05-051	0.25	3.4	67.7	10.1	5.1	99.3	14.9
ATCC 25923	0.06	1.4	116.2	17.4	1.8	147.3	22.1
04-154	0.125	0.8	27.6	4.1	1.8	70.4	10.6
04-045	0.25	3.1	61.9	9.29	4.7	91.2	13.7
Mean	**0.24**	**6.2**	**133.1**	**20**	**9.9**	**230.4**	**34.6**
Median	**0.25**	**6.4**	**116.2**	**17.4**	**9.5**	**173.2**	**26**
SD	**0.14**	**4.2**	**85.9**	**12.9**	**6.3**	**165.2**	**24.8**

[a] SD, static dose; tAUC/MIC, total drug AUC/MIC; fAUC/MIC, free drug (non-protein-bound) AUC/MIC. The means, medians, and static doses are shown in boldface type.

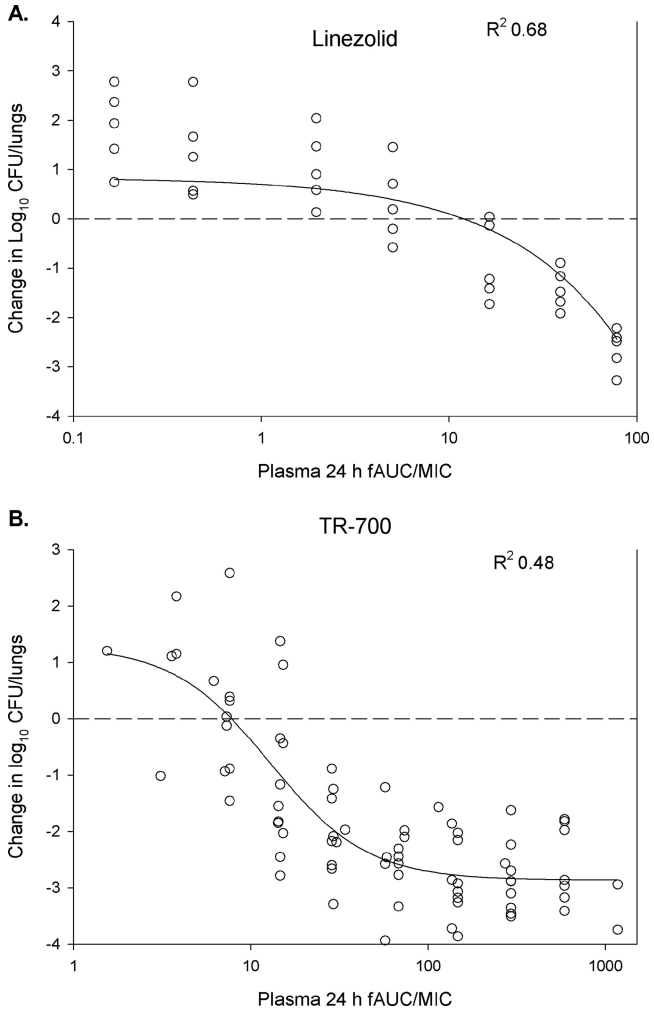

FIG 3 Relationship between linezolid (A) and TR-700 (B) plasma 24-h fAUC/MIC ratios and *in vivo* efficacy against multiple strains of *S. aureus* (5 and 11 strains, respectively). Mice were treated with 2-fold increasing concentrations of either linezolid or TR-701 given every 12 h over a 24-h treatment period. Each symbol represents the geometric mean in the change of organism burden from the start of therapy in the lungs of three mice. The dashed horizontal line represents the burden in the lungs at the start of therapy. Symbols below the line represent organism reduction compared to the start of therapy. Symbols above the line represent organism growth. The sigmoid lines represent the best-fit curves. R^2 is the coefficient of determination.

extensively examined, few studies have attempted to identify the AUC/MIC magnitude or target associated with efficacy in treatment against MSSA or MRSA. In an *in vivo* study of linezolid using a neutropenic murine thigh infection model, the PD index AUC/MIC provided the best correlation with efficacy and the static dose target was a fAUC/MIC of 58 (8). A single clinical PK/PD study examined linezolid efficacy in patients with MRSA cellulitis, bacteremia, and pneumonia (44). Clinical success was more common when the linezolid plasma fAUC/MIC value was near 30. More recently, the murine thigh infection model was used to explore the treatment efficacy of TR-701 against a single MRSA isolate (35). Similar to linezolid, the AUC/MIC ratio was the predictive index for efficacy, and net stasis in infectious burden was noted at a fAUC/MIC of 43 at the 24-h study endpoint.

The AUC/MIC stasis target identified in the current staphylococcal pneumonia studies was 2- to 4-fold lower than those reported in previous studies for both linezolid and TR-700 in soft tissue models. The stasis fAUC/MIC target in this study against nearly a dozen staphylococcal isolates was a value near 20. The similarity of the fAUC/MIC targets for both compounds when considering unbound drug (binding of 30% for linezolid versus 85% for TR-700) highlights the relevance of protein binding consideration when comparing PK/PD relationships across compounds within a similar mechanistic class (2, 17). The TR-700 fAUC/MIC magnitude associated with the 1-log-unit killing endpoint was only 34.6. The mechanistic explanation for the difference in PD targets in this lung model compared to previous soft tissue models is not entirely clear. The designs of each of these studies were similar in many ways, including the mouse species, drug exposures (PK), and the neutropenic state of immunosuppression. One small difference was the level of protein binding utilized for calculating free drug (non-protein-bound) exposures. The current study used 85% as the protein-bound fraction, whereas the previous study used 80% (35). Accounting for this difference alone would make the fAUC/MIC PD targets more congruent. Another key difference between the current and previous studies is the infection site. One intuitive theory to explain the discrepancy is the differential penetration of the oxazolidinones into the lung infection site (12, 16, 24, 26, 55). For example, at multiple time points after administration of linezolid (600 mg per os [p.o.]) twice a day (BID) for 2.5 days to humans, bronchoscopic examination of epithelial lining fluid (ELF) linezolid concentrations revealed 2.4- to 4.2-fold-higher concentrations of drug in ELF than in plasma (16). Similar results have been demonstrated with TR-700 with 40-fold-higher accumulation of active drug in ELF than in plasma (26). This PK difference at the infection site is a plausible explanation for the lower PD targets for oxazolidinones in pulmonary models compared to soft tissue models.

The majority of antimicrobial PD investigations have shown that the PD target is similar in treatment of organisms exhibiting drug resistance. We explored this tenet by study of multiple *S. aureus* strains with beta-lactam, macrolide, and lincosamide resistance mechanisms. The treatment fAUC/MIC targets were congruent across these strain genotypes as previously described for other drug classes (4–7, 47).

A valuable application of preclinical PD studies is the ability to translate the results from preclinical animal model studies into the clinical realm to predict whether certain drug exposures in patients are likely to be successful for a given organism, site of infection, and MIC distribution. PK studies of healthy volunteers have been recently reported with TR-701 (10, 11, 39, 42). Oral doses of 200 mg once a day produced an AUC between 22 and 26 mg · h/liter, whereas oral doses of 400 mg once daily produced an AUC between 54 and 56 mg · h/liter (10, 39, 42). If one considers the free drug AUC associated with these doses, the highest MIC for which a stasis fAUC/MIC target of 20 would be achieved is approximately 0.5 mg/liter for a 400-mg once-daily regimen. The MIC ceiling associated with the 1-log-unit kill PD targets would be an MIC of 0.25 mg/liter. *In vitro* surveillance study with TR-700 for *S. aureus* has identified an MIC_{50} and MIC_{90} of 0.25 and 0.5 mg/liter, respectively (9, 14, 48, 59).

In conclusion, the present study characterized the *in vivo* drug exposure response of a novel oxazolidinone, TR-701, in a neutropenic murine *S. aureus* pneumonia model. The results suggest that TR-701 would exhibit an efficacy similar to the efficacy of lin-

ezolid for *S. aureus* pneumonia. An unanswered question in the current study is whether TR-701 would be expected to have the same efficacy for a linezolid-resistant isolate, as has been suggested by *in vitro* results (32, 33, 46, 49). The results suggest further study of TR-701 in clinical trials of pneumonia due to *S. aureus* is warranted and may be especially useful given the increased burden of MSSA and MRSA pneumonia in the health care setting.

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REFERENCES

1. **Ambrose PG, et al.** 2007. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. Clin. Infect. Dis. **44**:79–86.
2. **Andes D.** 2003. In vivo pharmacodynamics of antifungal drugs in treatment of candidiasis. Antimicrob. Agents Chemother. **47**:1179–1186.
3. **Andes D, Craig WA.** 1998. In vivo activities of amoxicillin and amoxicillin-clavulanate against Streptococcus pneumoniae: application to breakpoint determinations. Antimicrob. Agents Chemother. **42**:2375–2379.
4. **Andes D, Craig WA.** 2007. In vivo pharmacodynamic activity of the glycopeptide dalbavancin. Antimicrob. Agents Chemother. **51**:1633–1642.
5. **Andes D, Craig WA.** 2006. Pharmacodynamics of a new streptogramin, XRP 2868, in murine thigh and lung infection models. Antimicrob. Agents Chemother. **50**:243–249.
6. **Andes D, Craig WA.** 2003. Pharmacodynamics of the new des-f(6)-quinolone garenoxacin in a murine thigh infection model. Antimicrob. Agents Chemother. **47**:3935–3941.
7. **Andes D, Craig WA.** 2002. Pharmacodynamics of the new fluoroquinolone gatifloxacin in murine thigh and lung infection models. Antimicrob. Agents Chemother. **46**:1665–1670.
8. **Andes D, van Ogtrop ML, Peng J, Craig WA.** 2002. In vivo pharmacodynamics of a new oxazolidinone (linezolid). Antimicrob. Agents Chemother. **46**:3484–3489.
9. **Betriu C, et al.** 2010. Comparative activities of TR-700 (torezolid) against staphylococcal blood isolates collected in Spain. Antimicrob. Agents Chemother. **54**:2212–2215.
10. **Bien P, et al.** 2008. Human pharmacokinetics of TR-700 after ascending single oral doses of the prodrug TR-701, a novel oxazolidinone antibiotic, abstr F1-2063. Abstr. 48th Annu. Intersci. Conf. Antimicrob. Agents Chemother. (ICAAC)-Infect. Dis. Soc. Am. (IDSA) 46th Annu. Meet. American Society for Microbiology and Infectious Diseases Society of America, Washington, DC.
11. **Bien P, Prokocimer P, Munoz KA, Bethune C.** 2010. Absolute bioavailability of TR-701 FA and pharmacokinetics after single and multiple dose intravenous administration in healthy adult subjects, abstr A1-013. Abstr. 50th Annu. Intersci. Conf. Antimicrob. Agents Chemother., Boston, MA. American Society for Microbiology, Washington, DC.
12. **Boselli E, et al.** 2005. Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. Crit. Care Med. **33**:1529–1533.
13. **Boucher HW, Corey GR.** 2008. Epidemiology of methicillin-resistant Staphylococcus aureus. Clin. Infect. Dis. **46**(Suppl. 5):S344–S349.
14. **Brown SD, Traczewski MM.** 2010. Comparative in vitro antimicrobial activities of torezolid (TR-700), the active moiety of a new oxazolidinone, torezolid phosphate (TR-701), determination of tentative disk diffusion interpretive criteria, and quality control ranges. Antimicrob. Agents Chemother. **54**:2063–2069.
15. **Clinical and Laboratory Standards Institute (CLSI).** 2009. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standards - eighth edition. CLSI document M07-A8. Clinical and Laboratory Standards Institute, Wayne, PA.
16. **Conte JE, Jr, Golden JA, Kipps J, Zurlinden E.** 2002. Intrapulmonary pharmacokinetics of linezolid. Antimicrob. Agents Chemother. **46**:1475–1480.
17. **Craig WA.** 1998. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin. Infect. Dis. **26**:1–10.
18. **Craig WA, Andes DR, Stamstad T.** 2010. In vivo pharmacodynamics of new lipopeptide MX-2401. Antimicrob. Agents Chemother. **54**:5092–5098.
19. **David MZ, Daum RS.** 2010. Community-associated methicillin-resistant Staphylococcus aureus: epidemiology and clinical consequences of an emerging epidemic. Clin. Microbiol. Rev. **23**:616–687.
20. **Diekema DJ, et al.** 2001. Survey of infections due to Staphylococcus species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997–1999. Clin. Infect. Dis. **32**(Suppl. 2):S114–S132.
21. **Drusano GL.** 2004. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat. Rev. Microbiol. **2**:289–300.
22. **Drusano GL, Liu W, Kulawy R, Louie A.** 2011. Impact of granulocytes on the antimicrobial effect of tedizolid in a mouse thigh infection model. Antimicrob. Agents Chemother. **55**:5300–5305.
23. **Gentry-Nielsen MJ, Olsen KM, Preheim LC.** 2002. Pharmacodynamic activity and efficacy of linezolid in a rat model of pneumococcal pneumonia. Antimicrob. Agents Chemother. **46**:1345–1351.
24. **Honeybourne D, Tobin C, Jevons G, Andrews J, Wise R.** 2003. Intrapulmonary penetration of linezolid. J. Antimicrob. Chemother. **51**:1431–1434.
25. **Hota B, et al.** 2011. Predictors of clinical virulence in community-onset methicillin-resistant Staphylococcus aureus infections: the importance of USA300 and pneumonia. Clin. Infect. Dis. **53**:757–765.
26. **Housman ST, et al.** 2012. Pulmonary disposition of tedizolid following administration of once-daily oral 200-milligram tedizolid phosphate in healthy adult volunteers. Antimicrob. Agents Chemother. **56**:2627–2634.
27. **Keel RA, Tessier PR, Crandon JL, Nicolau DP.** 2012. Comparative efficacy of human simulated exposures of tedizolid and linezolid against Staphylococcus aureus in the murine thigh infection model. Antimicrob. Agents Chemother. **56**:4403–4407.
28. **Klein E, Smith DL, Laxminarayan R.** 2007. Hospitalizations and deaths caused by methicillin-resistant Staphylococcus aureus, United States, 1999–2005. Emerg. Infect. Dis. **13**:1840–1846.
29. **Klevens RM, et al.** 2007. Invasive methicillin-resistant Staphylococcus aureus infections in the United States. JAMA **298**:1763–1771.
30. **Kollef MH, Rello J, Cammarata SK, Croos-Dabrera RV, Wunderink RG.** 2004. Clinical cure and survival in Gram-positive ventilator-associated pneumonia: retrospective analysis of two double-blind studies comparing linezolid with vancomycin. Intensive Care Med. **30**:388–394.
31. **Kreienbuehl L, Charbonney E, Eggimann P.** 2011. Community-acquired necrotizing pneumonia due to methicillin-sensitive Staphylococcus aureus secreting Panton-Valentine leukocidin: a review of case reports. Ann. Intensive Care **1**:52. doi:10.1186/2110-5820-1-52.
32. **Locke JB, Hilgers M, Shaw KJ.** 2009. Mutations in ribosomal protein L3 are associated with oxazolidinone resistance in staphylococci of clinical origin. Antimicrob. Agents Chemother. **53**:5275–5278.
33. **Locke JB, Hilgers M, Shaw KJ.** 2009. Novel ribosomal mutations in Staphylococcus aureus strains identified through selection with the oxazolidinones linezolid and torezolid (TR-700). Antimicrob. Agents Chemother. **53**:5265–5274.
34. **Louie A, Liu W, Deziel MR, Drusano GL.** 2004. Pharmacodynamics of linezolid in a neutropenic mouse thigh model of *Staphylococcus aureus* infection, abstr A-1805. Abstr. 44th Annu. Intersci. Conf. Antimicrob. Agents Chemother. American Society for Microbiology, Washington, DC.
35. **Louie A, Liu W, Kulawy R, Drusano GL.** 2011. In vivo pharmacodynamics of torezolid phosphate (TR-701), a new oxazolidinone antibiotic, against methicillin-susceptible and methicillin-resistant Staphylococcus aureus in a mouse thigh infection model. Antimicrob. Agents Chemother. **55**:3453–3460.
36. **Luna CM, et al.** 2009. Effect of linezolid compared with glycopeptides in methicillin-resistant Staphylococcus aureus severe pneumonia in piglets. Chest **135**:1564–1571.
37. **MacGowan AP.** 2003. Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections. J. Antimicrob. Chemother. **51**(Suppl. 2):ii17–ii25.
38. **Martinez-Olondris P, et al.** 2012. Efficacy of linezolid compared to vancomycin in an experimental model of pneumonia induced by methicillin-resistant Staphylococcus aureus in ventilated pigs. Crit. Care Med. **40**:162–168.
39. **Munoz KA, et al.** 2010. Improved pharmacokinetics of the novel oxazolidinone antibiotic torezolid phosphate compared to linezolid in healthy subjects, abstr P-1594. 20th Eur. Cong. Clin. Microbiol. Infect. Dis., Vienna, Austria. European Society of Clinical Microbiology and Infectious Diseases, Basel, Switzerland.

40. **Pfaller MA, et al.** 2006. Correlation of MIC with outcome for Candida species tested against voriconazole: analysis and proposal for interpretive breakpoints. J. Clin. Microbiol. **44**:819–826.
41. **Pfaller MA, Diekema DJ, Sheehan DJ.** 2006. Interpretive breakpoints for fluconazole and Candida revisited: a blueprint for the future of antifungal susceptibility testing. Clin. Microbiol. Rev. **19**:435–447.
42. **Prokocimer P, et al.** 2008. Human pharmacokinetics of the prodrug TR-701 and TR-700, its active moiety, after multiple oral doses of TR-701, a novel oxazolidinone, abstr F1-2064. Abstr. 48th Annu. Intersci. Conf. Antimicrob. Agents Chemother. (ICAAC)-Infect. Dis. Soc. Am. (IDSA) 46th Annu. Meet. American Society for Microbiology and Infectious Diseases Society of America, Washington, DC.
43. **Prokocimer P, et al.** 2011. Phase 2, randomized, double-blind, dose-ranging study evaluating the safety, tolerability, population pharmacokinetics, and efficacy of oral torezolid phosphate in patients with complicated skin and skin structure infections. Antimicrob. Agents Chemother. **55**:583–592.
44. **Rayner CR, Forrest A, Meagher AK, Birmingham MC, Schentag JJ.** 2003. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin. Pharmacokinet. **42**: 1411–1423.
45. **Rex JH, et al.** 1997. Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of in vitro-in vivo correlation data for fluconazole, itraconazole, and Candida infections. Subcommittee on Antifungal Susceptibility Testing of the National Committee for Clinical Laboratory Standards. Clin. Infect. Dis. **24**:235–247.
46. **Rodriguez-Avial I, et al.** 2012. In vitro activity of tedizolid (TR-700) against linezolid-resistant staphylococci. J. Antimicrob. Chemother. **67**: 167–169.
47. **Safdar N, Andes D, Craig WA.** 2004. In vivo pharmacodynamic activity of daptomycin. Antimicrob. Agents Chemother. **48**:63–68.
48. **Schaadt R, Sweeney D, Shinabarger D, Zurenko G.** 2009. In vitro activity of TR-700, the active ingredient of the antibacterial prodrug TR-701, a novel oxazolidinone antibacterial agent. Antimicrob. Agents Chemother. **53**:3236–3239.
49. **Shaw KJ, et al.** 2008. In vitro activity of TR-700, the antibacterial moiety of the prodrug TR-701, against linezolid-resistant strains. Antimicrob. Agents Chemother. **52**:4442–4447.
50. **Shorr AF, et al.** 2006. Morbidity and cost burden of methicillin-resistant Staphylococcus aureus in early onset ventilator-associated pneumonia. Crit. Care **10**:R97. doi:10.1186/cc4934.
51. **Slatter JG, et al.** 2002. Pharmacokinetics, toxicokinetics, distribution, metabolism and excretion of linezolid in mouse, rat and dog. Xenobiotica **32**:907–924.
52. **Stefani S, Varaldo PE.** 2003. Epidemiology of methicillin-resistant staphylococci in Europe. Clin. Microbiol. Infect. **9**:1179–1186.
53. **Strukova EN, et al.** 2009. Linezolid pharmacodynamics with Staphylococcus aureus in an in vitro dynamic model. Int. J. Antimicrob. Agents **33**:251–254.
54. **Styers D, Sheehan DJ, Hogan P, Sahm DF.** 2006. Laboratory-based surveillance of current antimicrobial resistance patterns and trends among Staphylococcus aureus: 2005 status in the United States. Ann. Clin. Microbiol. Antimicrob. **5**:2. doi:10.1186/1476-0711-5-2.
55. **Tessier PR, Keel RA, Hagihara M, Crandon JL, Nicolau DP.** 2012. Comparative in vivo efficacies of epithelial lining fluid exposures of tedizolid, linezolid, and vancomycin for methicillin-resistant Staphylococcus aureus in a mouse pneumonia model. Antimicrob. Agents Chemother. **56**:2342–2346.
56. **Watanabe A, et al.** 2012. Usefulness of linezolid in the treatment of hospital-acquired pneumonia caused by MRSA: a prospective observational study. J. Infect. Chemother. **18**:160–168.
57. **Wunderink RG, et al.** 2012. Linezolid in methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a randomized, controlled study. Clin. Infect. Dis. **54**:621–629.
58. **Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH.** 2003. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant Staphylococcus aureus nosocomial pneumonia. Chest **124**:1789–1797.
59. **Yum JH, et al.** 2010. Comparative in vitro activities of torezolid (DA-7157) against clinical isolates of aerobic and anaerobic bacteria in South Korea. Antimicrob. Agents Chemother. **54**:5381–5386.