

Comparative Potency of Oxazolidinones Tedizolid (TR-700) and Linezolid Against Target Gram-Positive Pathogens in the US from 2009-2010

E-1324

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Abstract

Background: Resistance and multidrug resistance among Gram-positive pathogens, in particular *S. aureus*, has limited the utility of many common antibacterials. Decreased susceptibility to daptomycin, linezolid, and vancomycin remains infrequent, but potential for growing resistance is a significant concern. Tedizolid (TR-700), formerly known as torezolid, is an oxazolidinone with potent activity against gram-positive pathogens currently undergoing trials for the treatment of acute bacterial skin and skin structure infections (ABSSSI). This study reports the current susceptibility of target gram-positive pathogens from the US, comparing the activity profiles of TR-700 and linezolid.

Methods: 1,248 *S. aureus*, 50 *E. faecalis*, 38 *E. faecium*, 101 *S. pyogenes*, 28 *S. agalactiae*, and 29 Anginosus Group Streptococci (AGS) clinical isolates from 93 distributed sites from 2009-2010 were tested by broth microdilution per CLSI guidelines for susceptibility to TR-700, linezolid, and comparators. Resistance to ≥3 classes of agent (excluding beta-lactams) defined MDR among *S. aureus*.

Results: TR-700 and linezolid (LZD) activity against evaluated isolates by phenotype is noted in the table below:

Organism	Phenotype	N	TR-700		LZD	
			MIC ₅₀	MIC ₉₀	MIC ₅₀	MIC ₉₀
<i>S. aureus</i>	all	1248	0.25	0.5	2	2
	MRSA	722 (58%)	0.25	0.5	2	2
	MDR	266 (21%)	0.25	0.5	2	2
beta-hemolytic streptococci	all	129	0.25	0.25	0.5	1
	EryR	21 (16%)	0.25	0.25	0.5	1
AGS	all	28	0.12	0.25	0.5	1
Enterococci	all	88	0.25	0.5	2	2
	VRE	27 (31%)	0.25	0.5	2	2

Against the only linezolid-resistant *S. aureus* and *E. faecium* (TR-700 MICs of 16 and 32 mg/mL, respectively), TR-700 had an MIC of 1 and 4 mg/mL, respectively.

Conclusions: Based on MIC₅₀/MIC₉₀, TR-700 was 4-8 fold more potent than linezolid. The activity profiles of TR-700 and linezolid were not impacted by resistance common among the evaluated pathogens (e.g. MRSA, VRE, etc.), and TR-700 maintained activity against linezolid-resistant isolates. The activity profile of TR-700 highlights its potential for the treatment of Gram-positive infections such as ABSSSI, though emerging resistance warrants continued surveillance for all developmental and approved oxazolidinones.

Background

S. aureus is a prevalent pathogen associated with acute bacterial skin and skin structure infections (ABSSSI), bacteremia, and respiratory infections. The emergence of MRSA, particularly multidrug-resistant strains in both the inpatient and outpatient populations, underscores the need to ensure the continued availability of new and effective anti-gram positive agents. This is especially true with the recognition of staphylococci that have reduced susceptibility to vancomycin, linezolid, and daptomycin.

Tedizolid (TR-700), formerly known as torezolid, is a novel oxazolidinone currently undergoing clinical development for the treatment of acute bacterial skin and skin structure infections. As such, it is imperative that careful monitoring of its activity against a robust collection of target pathogens is conducted on a regular basis, especially given the propensity that *S. aureus* has demonstrated to develop resistance.

To that end this current study was conducted to analyze the *in vitro* activity of TR-700 relative to other key agents against a recent collection of *S. aureus* isolates and other target species collected across the USA.

Methods

- S. aureus*, *E. faecalis*, *E. faecium*, *S. pyogenes* (GAS), *S. agalactiae* (GBS), and Anginosus Group Streptococci (AGS) clinical isolates were collected from 93 sites distributed across the USA in 2009-2010
- Isolates were tested centrally (Eurofins Medinet) for susceptibility to TR-700, linezolid (LZD) and other comparators by broth microdilution in accordance with CLSI guidelines
- For *S. aureus*, multidrug resistance (MDR) was defined as resistance to ≥3 different classes of agent among clindamycin, erythromycin (ERY), gentamicin, levofloxacin, and trimethoprim/sulfamethoxazole

Results

TABLE 1. Comparative Activities of TR-700 and Linezolid Against Key Gram-Positive Pathogens

Organism	Drug	MIC (µg/mL)				%S
		range	mode	MIC ₅₀	MIC ₉₀	
<i>S. aureus</i> (N=1,248)	TR-700	0.06-1	0.25	0.25	0.5	-
	Linezolid	0.5-16	2	2	2	99.9
<i>S. pyogenes</i> (N=101)	TR-700	0.12-0.25	0.25	0.25	0.25	-
	Linezolid	0.5-1	1	1	1	100.0
<i>S. agalactiae</i> (N=28)	TR-700	0.12-0.25	0.25	0.25	0.25	-
	Linezolid	0.5-1	0.5	0.5	1	100.0
AGS (N=29)	TR-700	≤0.015-0.25	0.12	0.12	0.25	-
	Linezolid	≤0.06-1	0.5	0.5	0.5	100.0
<i>E. faecalis</i> (N=50)	TR-700	0.12-0.5	0.25	0.25	0.5	-
	Linezolid	0.25-2	1	1	2	100.0
<i>E. faecium</i> (N=38)	TR-700	0.25-4	0.25	0.25	0.5	-
	Linezolid	1-32	2	2	2	97.4

TABLE 2. Comparative Activities of TR-700 and Linezolid Against Key Resistance Phenotypes

Organism	Phenotype	Drug	MIC (µg/mL)				%S
			range	mode	MIC ₅₀	MIC ₉₀	
<i>S. aureus</i>	MSSA (N=526)	TR-700	0.06-0.5	0.25	0.25	0.5	-
		Linezolid	0.5-4	2	2	2	100.0
	MRSA (N=722)	TR-700	0.06-1	0.25	0.25	0.5	-
		Linezolid	0.5-16	2	2	2	99.9
MDR (N=265)	TR-700	0.06-1	0.25	0.25	0.5	-	
	Linezolid	0.5-16	2	2	2	99.6	
Beta-hemolytic streptococci	ERY S (N=107)	TR-700	0.12-0.25	0.25	0.25	0.25	-
		Linezolid	0.5-1	1	1	1	100.0
ERY NS (N=22)	TR-700	0.12-0.25	0.25	0.25	0.25	-	
	Linezolid	0.5-1	0.5	0.5	1	100.0	
Enterococci	VAN S (N=61)	TR-700	0.012-0.5	0.25	0.25	0.5	-
		Linezolid	0.5-2	2	1	2	100.0
	VAN NS (N=27)	TR-700	0.12-4	0.25	0.25	0.5	-
		Linezolid	0.25-32	2	2	2	96.4

FIGURE 1. TR-700 and Linezolid MIC Distributions for *S. aureus* According to Methicillin Status

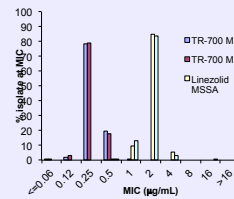


FIGURE 2. Scatterplot Analysis of TR-700 and Linezolid MICs Against *S. aureus*

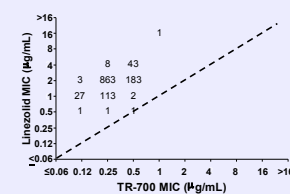


FIGURE 3. TR-700 and Linezolid MIC Distributions for Beta-Hemolytic Streptococci According to Macrolide Status

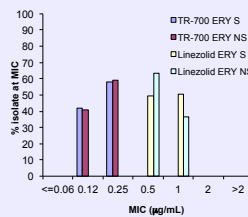


FIGURE 4. Scatterplot Analysis of TR-700 and Linezolid MICs Against Beta-Hemolytic Streptococci

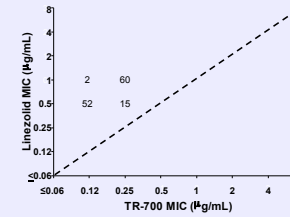


FIGURE 5. TR-700 and Linezolid MIC Distributions for Enterococci According to Vancomycin Status

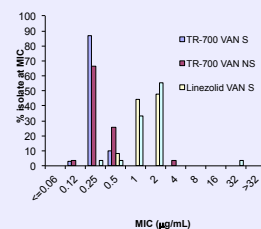
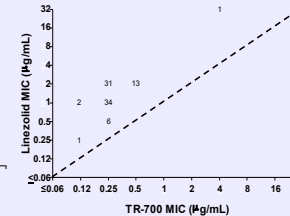


FIGURE 6. Scatterplot Analysis of TR-700 and Linezolid MICs Against Enterococci



- Based on MIC₉₀s for all organism groups tested, TR-700 was two- to four-fold more potent than LZD (Table 1).
- The differences in potency between TR-700 and LZD were essentially maintained when MIC₅₀s were evaluated according to key resistance phenotypes (Table 2). For both MRSA and MDR *S. aureus*, TR-700 was four-fold more potent than LZD.
- Further evaluation of the relative MIC potencies of TR-700 and LZD demonstrate that the differences in MIC distributions for the two agents were maintained for both MRSA and MSSA (Figure 1).
- Scatterplot analysis for all *S. aureus* (Figure 2) demonstrated that the most common phenotype was strains having a TR-700 MIC of 0.25 µg/ml and a LZD MIC of 2 µg/ml (an eight-fold difference). The second most common phenotype was strains with a TR-700 MIC of 0.5 µg/ml and a LZD MIC of 2 µg/ml.
- Similarly for beta-hemolytic streptococci the differences in MIC distributions for TR-700 and LZD were maintained for both macrolide-susceptible and -resistant strains (Figure 3); by scatterplot analysis the two most common phenotypes had TR-700 MICs of 0.12 µg/ml and LZD MICs of 0.5 µg/ml, and TR-700 MICs of 0.25 µg/ml and LZD MICs of 1 µg/ml (Figure 4).
- The relative activities of TR-700 and LZD against enterococci were not notably impacted by vancomycin susceptibility status (Figure 5) and by scatterplot analysis. For enterococci the most common phenotypes were strains with a TR-700 MICs of 0.25 µg/ml and a LZD MICs of either 1 or 2 µg/ml (Figure 6).

Conclusions

- Based on MIC analysis TR-700 was two to four-fold more potent than LZD for all of the gram-positive organism groups studied.
- The potential clinical significance of the potency differences will be better understood as clinical trial data and PK/PD data are analyzed going forward.
- Nonetheless, TR-700 has demonstrated potent *in vitro* activity against the full spectrum of gram-positive organisms associated with skin and skin structure infections. From this perspective tedizolid's therapeutic potential is clearly apparent.
- With the emergence of oxazolidinone resistance mediated by *crf* and ribosomal modifications it is imperative that the level of potency of TR-700 continue to be monitored going forward.

Acknowledgement

This study was supported by a grant from Trius Therapeutics.