

Comparative *In vitro* Potency of Torezolid (TR-700) and Linezolid Against Key Gram-Positive Pathogens of European Origin (2009-2010)

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ABSTRACT

Objectives: Torezolid (TR-700) is an investigational oxazolidinone currently under development for the treatment of acute bacterial skin and skin structure infections (ABSSSI). Target ABSSSI pathogens of torezolid include *S. aureus*, beta-hemolytic streptococci, and enterococci. As part of its development, it is important to establish the activity profile of torezolid relative to that of linezolid, the only currently marketed oxazolidinone. This study was conducted to analyze such activity as it pertains to European isolates of target skin pathogens.

Methods: Non-duplicate, non-consecutive clinical isolates of *S. aureus* (N=444), *E. faecium* (N=33), *E. faecalis* (N=25), *S. pyogenes* (GAS; N=50), *S. agalactiae* (GBS; N=32), and Group C/F/G streptococci (C/F/G; N=10) were collected from 18 sites distributed across nine European countries from 2009-2010. Isolates underwent susceptibility testing against torezolid, linezolid, and other relevant comparators in accordance with CLSI M7 and M100 guidelines at a central laboratory (Eurofins Medinet, Chantilly, VA).

Results: The MIC₅₀ and MIC₉₀ (mg/L) of torezolid and linezolid against the evaluated pathogens are presented in Table 1. Torezolid had a MIC₅₀ and MIC₉₀ 4-8 fold lower than that of linezolid across gram-positive species. Among *S. aureus*, 20% were MRSA; 85% of *S. aureus* had torezolid MICs 4-fold lower than linezolid while 15% had torezolid MICs 8-fold lower than linezolid. Of the beta-hemolytic streptococci, 16% were resistant to macrolides. 28% of beta-hemolytic streptococci had torezolid MICs 4-fold lower than linezolid and 70% had torezolid MICs 8-fold lower than linezolid. Among enterococci, of which 7% were vancomycin non-susceptible, 54% of isolates had torezolid MICs that were 4-fold lower than linezolid and 46% of isolates had torezolid MICs that were 8-fold lower than linezolid.

Conclusions: These data demonstrate that the *in vitro* potency of torezolid (based on MICs) against key gram-positive pathogens is several-fold greater than that of linezolid. It will be of interest to determine the level of torezolid activity against linezolid non-susceptible isolates, thus continued surveillance monitoring of oxazolidinone susceptibility is essential.

BACKGROUND

Torezolid (TR-700) is a novel oxazolidinone currently undergoing clinical trials in the US and Europe for the treatment of acute bacterial skin and skin structure infections

As part of its ongoing clinical development, it is important to generate current surveillance data against target pathogens collected from areas for which the drug is anticipated to be used

This study reports the current *in vitro* activity profile of torezolid as it compares to in class comparator linezolid against target Gram-positive skin and skin structure pathogens collected throughout Europe in 2009-2010

METHODS

Non-duplicate, non-consecutive clinical isolates of *S. aureus* (N=479), beta-hemolytic streptococci (*S. pyogenes* (N=50), *S. agalactiae* (N=32), and Group C/F/G streptococci (N=10)) and enterococci (*E. faecalis* (N=26), *E. faecium* (N=33)) were collected from 2009-2010 from 18 sites distributed across 9 European countries

Isolates were shipped to Eurofins (Chantilly, VA) where they underwent confirmatory identification and susceptibility testing by broth microdilution in accordance with the most current CLSI M7 and M100 guidance documents

Of the evaluated isolates, 38% were from respiratory tract, 34% were from blood, 21% were from skin/wound, 5% were from urine, and 2% were from other/unknown specimen sources; 78% were from inpatients (28% of which were confined to the ICU) and 22% were from outpatients

TABLE 1. Current *in vitro* activity profile of torezolid and linezolid among target skin pathogens from Europe (2009-2010)

Organism	Drug	MIC (mg/L)				%S
		range	mode	MIC ₅₀	MIC ₉₀	
<i>S. aureus</i> (N=479)	Torezolid	0.12-2	0.25	0.25	0.5	100.0
	Linezolid	0.5-4	2	2	4	100.0
<i>S. pyogenes</i> (N=50)	Torezolid	0.06-0.25	0.12	0.12	0.25	100.0
	Linezolid	0.5-1	0.5	0.5	1	100.0
<i>S. agalactiae</i> (N=32)	Torezolid	0.12-0.5	0.25	0.25	0.25	100.0
	Linezolid	0.5-1	1	1	1	100.0
Group C/F/G streptococci (N=10)	Torezolid	<=0.015-0.12	0.06	0.06	0.12	100.0
	Linezolid	0.12-1	0.5	0.5	0.5	100.0
<i>E. faecalis</i> (N=26)	Torezolid	0.25-0.5	0.25	0.25	0.5	100.0
	Linezolid	1-2	2	2	2	100.0
<i>E. faecium</i> (N=33)	Torezolid	0.03-0.5	0.25	0.25	0.5	100.0
	Linezolid	0.12-2	2	2	2	100.0

FIGURE 1. Torezolid and linezolid MIC distribution against *S. aureus* (N=479)

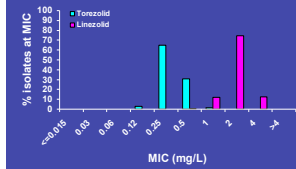


FIGURE 4. MIC distribution of torezolid and linezolid against MSSA (N=383) and MRSA (N=96)

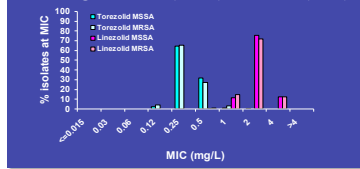


FIGURE 2. Torezolid and linezolid MIC distribution against beta-hemolytic streptococci (N=92)

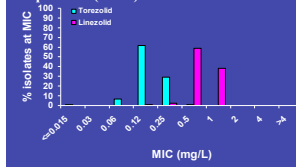


FIGURE 5. MIC distribution of torezolid and linezolid against macrolide susceptible (N=77) and non-susceptible (N=15) beta-hemolytic streptococci

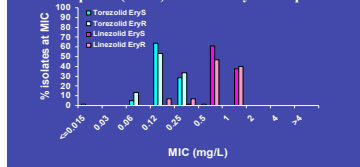


FIGURE 3. Torezolid and linezolid MIC distribution against enterococci (N=59)

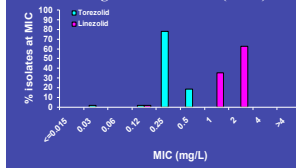


TABLE 2. *In vitro* activity of torezolid and linezolid against target skin pathogens by phenotype

Organism	Phenotype	Drug	MIC (mg/L)				%S
			range	mode	MIC ₅₀	MIC ₉₀	
<i>S. aureus</i>	MSSA (N=383)	Torezolid	0.12-2	0.25	0.25	0.5	100.0
		Linezolid	0.5-4	2	2	4	100.0
MRSA (N=96)	Torezolid	Torezolid	0.12-2	0.25	0.25	0.5	100.0
		Linezolid	0.5-4	2	2	4	100.0
Beta-hemolytic streptococci	Macrolide S (N=77)	Torezolid	0.06-0.25	0.12	0.12	0.25	100.0
		Linezolid	0.25-1	0.5	0.5	1	100.0
Macrolide NS (N=15)	Torezolid	Torezolid	0.06-0.25	0.12	0.12	0.25	100.0
		Linezolid	0.12-1	0.5	0.5	1	100.0
Enterococci	VAN S (N=15)	Torezolid	0.03-0.5	0.25	0.25	0.5	100.0
		Linezolid	0.12-2	2	2	2	100.0
VAN NS (N=4)	Torezolid	Torezolid	0.12-0.5	0.25	0.25	0.5	100.0
		Linezolid	1-2	2	2	2	100.0

NR: not applicable

FIGURE 6. Torezolid MICs vs. Linezolid MICs against *S. aureus* (N=479)

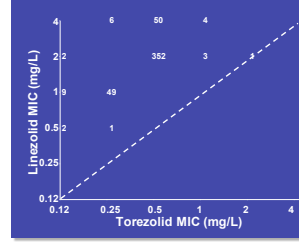


FIGURE 7. Torezolid MICs vs. Linezolid MICs against beta-hemolytic streptococci (N=92)

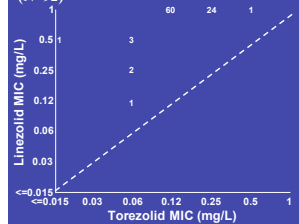
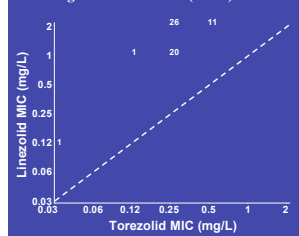


FIGURE 8. Torezolid MICs vs. Linezolid MICs against enterococci (N=59)



RESULTS

S. aureus

Torezolid had an MIC₉₀ of 0.5 mg/L, 8-fold lower than that of linezolid (4 mg/L)

By direct MIC to MIC comparison, 99% of *S. aureus* had torezolid MICs at least 4-fold lower than linezolid, with 14% having torezolid MICs at least 8-fold lower than linezolid

The activity of torezolid and linezolid was not impacted by methicillin resistance, which was observed to occur in 20% of collected isolates overall

Beta-hemolytic Streptococci

Torezolid had an MIC₉₀ of 0.25 mg/L against GAS and GBS, and 0.12 mg/L against Group C/F/G streptococci, 4-fold lower than that of linezolid (1 mg/L against GAS and GBS, 0.5 against Group C/F/G streptococci)

By direct MIC to MIC comparison, 98% of beta-hemolytic streptococci had torezolid MICs at least 4-fold lower than linezolid, with 70% having torezolid MICs at least 8-fold lower than linezolid

The activity of torezolid and linezolid was not impacted by macrolide resistance, which was observed to occur in 16% of collected isolates overall

Enterococci

Torezolid had an MIC₉₀ of 0.5 mg/L against *E. faecalis* and *E. faecium*, 4-fold lower than that of linezolid (2 mg/L)

By direct MIC to MIC comparison, 100% of enterococci had torezolid MICs at least 4-fold lower than linezolid, with 46% having torezolid MICs at least 8-fold lower than linezolid

The activity of torezolid and linezolid was not impacted by vancomycin resistance, which was observed to occur in 5% of collected isolates overall

CONCLUSIONS

Torezolid was 4-8 fold more potent *in vitro* than linezolid against evaluated Gram-positive skin pathogens collected in Europe

Though the clinical significance of the increased potency of torezolid relative to linezolid remains uncertain, the *in vitro* activity profile of torezolid highlights the potential of this agent as a therapeutic for resistant Gram-positive infections

With the recent emergence and spread of resistance to oxazolidinones mediated by *cfi* and ribosomal modification, continued surveillance of the activity of torezolid and linezolid against target pathogens is extremely important

Based on the above activity profile, further evaluation of torezolid activity against emerging linezolid resistant strains is of particular interest

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