

ABSTRACT

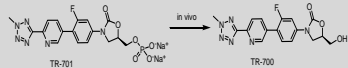
Background: TR-701 is the pro-drug of the microbiologically-active molecule TR-700, a novel oxazolidinone. TR-701 is orally absorbed and converted by phosphatases to the active form, achieving high bioavailability. The *in vitro* activity of TR-700 was evaluated against 359 clinical isolates of Gram-positive bacteria, including community-acquired MRSA (CA-MRSA) and strains resistant to linezolid (LZD). **Methods:** The test strains were recent clinical isolates from diverse sites in the US (70%) and Europe (30%). MIC assays were conducted using the CLSI reference broth microdilution method and the comparator agents LZD, daptomycin, and vancomycin. **Results:** The results for TR-700 compared to those of LZD are summarized below.

Organism (No.)	MIC Range		MIC ₅₀		MIC ₉₀	
	TR-700	LZD	TR-700	LZD	TR-700	LZD
MSSA (50)	0.25-0.5	1-4	0.5	2	0.5	4
MRSA (50)	0.25-1	2-4	0.5	2	0.5	4
CA-MRSA (25)	0.25-0.5	2-4	0.5	2	0.5	2
MSSE (25)	0.12-0.25	0.5-1	0.12	1	0.25	1
MRSE (25)	0.12-0.5	0.5-2	0.25	1	0.25	1
VSEfaecalis (18)	0.25-0.5	1-2	0.5	2	0.5	2
VREfaecalis (17)	0.5-1	1-4	0.5	2	1	2
VSEfaecium (12)	0.25-0.5	2	0.5	2	0.5	2
VREfaecium (25)	0.12-0.5	1-2	0.5	2	0.5	2
PSSP (18)	0.06-0.25	0.25-1	0.12	1	0.25	1
PRSP (11)	0.06-0.5	0.5-1	0.25	1	0.25	1
PRSP (16)	0.12-0.25	0.5-2	0.25	1	0.25	1
<i>S. pyogenes</i> (35)	0.25-0.5	1-2	0.25	1	0.5	2
<i>S. agalactiae</i> (20)	0.25-1	1-2	0.5	2	0.5	2

TR-700 was 4- to 8-fold more potent than LZD against staphylococci, and generally 4-fold more potent against the other organisms tested. **Conclusions:** TR-701 is a promising new oxazolidinone antibacterial agent with greater *in vitro* potency than LZD against clinically-important Gram-positive bacteria.

INTRODUCTION

TR-701 (formerly DA-70157, DA-7157), an oxazolidinone antibiotic, is an orally administered prodrug of the active molecule, TR-700. The prodrug TR-701 is orally absorbed and readily converted with high bioavailability to the active form TR-700. The conversion is mediated by phosphatases which are fairly ubiquitous enzymes in tissue and blood. The specificity of TR-701 for the different classes of phosphatases is not known.



The *in vitro* activity of TR-700 was previously demonstrated against bacterial clinical isolates that originated in South Korea (1,2). The purpose of this study was to assess the activity of TR-700 against recent clinical isolates from the United States and Europe.

The activity of TR-700 against Gram-positive pathogens with characterized resistance genes is the subject of a separate presentation at this meeting (see Shaw, K. et al. Presentation F1-1688).

MATERIALS & METHODS

TR-700 was provided by Trius Therapeutics. The comparator agents were linezolid (Pfizer), vancomycin (Sigma), daptomycin (Cubist), oxacillin sodium and penicillin G sodium (Fluka).

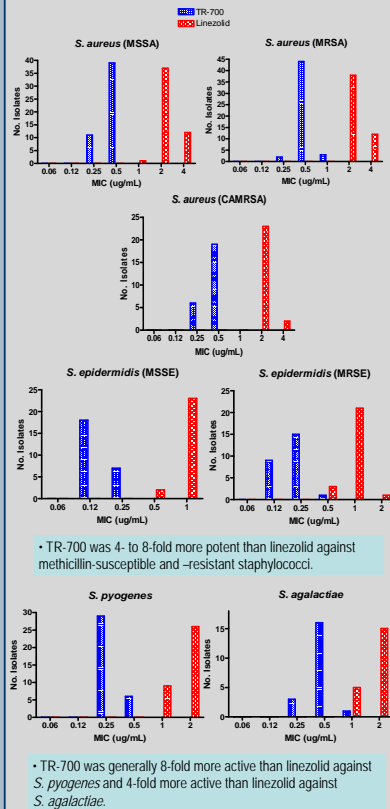
The test organisms for the assay were recent clinical isolates from diverse geographical centers. Approximately 70% of the isolates originated in the United States and 30% originated in Europe.

The MIC assay was conducted using the broth microdilution method as described by the Clinical and Laboratory Standards Institute (3). The CLSI quality control strains *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212 were tested in each set of assays to ensure the proper performance of the assay.

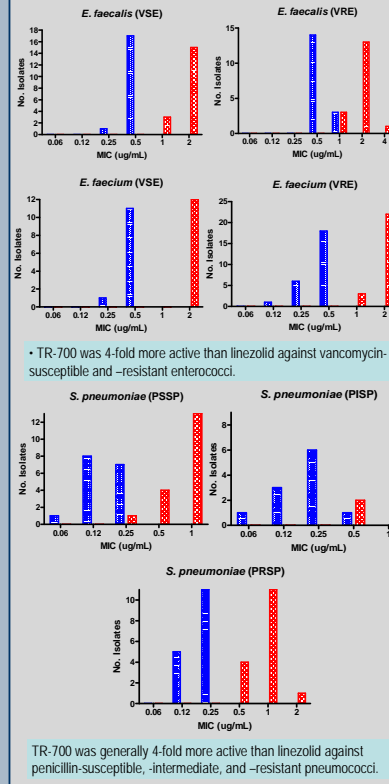
The test medium was Mueller Hinton II Broth (MHB II; Becton Dickinson, Sparks, MD). MHB II was supplemented with 2% lysed horse blood (Cleveland Scientific, Bath, OH) for growth of streptococci.

RESULTS

MIC results for TR-700 and linezolid are shown below.



RESULTS



DISCUSSION

- TR-700 and linezolid demonstrated potent activity against Gram-positive bacteria, including strains resistant to a variety of medically-important antibacterial agents
- For staphylococci, the MIC values for TR-700 were 4- to 8-fold lower than those for linezolid
- For enterococci, the MIC values for TR-700 were 4-fold lower than those for linezolid
- For streptococci, the MIC values for TR-700 were 4- to 8-fold lower than those for linezolid
- The MIC data were consistent with that previously reported for South Korean isolates
- TR-700 is a novel, potent oxazolidinone antibacterial agent that is a candidate for continued development

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