

Novel ribosomal mutations in Staphylococcus aureus strains identified through selection with the oxazolidinones linezolid and torezolid (TR-700)

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Locke JB, Hilgers M, Shaw KJ.

Trius Therapeutics, Inc., San Diego, CA 92121, USA.

TR-700 (torezolid), the active moiety of the novel oxazolidinone phosphate prodrug TR-701, is highly potent against gram-positive pathogens, including strains resistant to linezolid (LZD). Here we investigated the potential of *Staphylococcus aureus* strains ATCC 29213 (methicillin-susceptible *S. aureus* [MSSA]) and ATCC 33591 (methicillin-resistant *S. aureus* [MRSA]) to develop resistance to TR-700. The spontaneous frequencies of mutation of MSSA 29213 and MRSA 33591 resulting in reduced susceptibility to TR-700 at 2 x the MIC were 1.1×10^{-10} and 1.9×10^{-10} , respectively. These values are approximately 16-fold lower than the corresponding LZD spontaneous mutation frequencies of both strains. Following 30 serial passages in the presence of TR-700, the MIC for MSSA 29213 remained constant (0.5 microg/ml) while increasing eightfold (0.25 to 2.0 microg/ml) for MRSA 33591. Serial passage of MSSA 29213 and MRSA 33591 in LZD resulted in 64- and 32-fold increases in LZD resistance (2 to 128 microg/ml and 1 to 32 microg/ml, respectively). Domain V 23S rRNA gene mutations (*Escherichia coli* numbering) found in TR-700-selected mutants included T2500A and a novel coupled T2571C/G2576T mutation, while LZD-selected mutants included G2447T, T2500A, and G2576T. We also identified mutations correlating with decreased susceptibility to TR-700 and LZD in the *rplC* and *rplD* genes, encoding the 50S ribosomal proteins L3 and L4, respectively. L3 mutations included Gly152Asp, Gly155Arg, Gly155Arg/Met169Leu, and DeltaPhe127-His146. The only L4 mutation detected was Lys68Gln. TR-700 maintained a fourfold or greater potency advantage over LZD against all strains with ribosomal mutations. These data bring to light a variety of novel and less-characterized mutations associated with *S. aureus* resistance to oxazolidinones and demonstrate the low resistance potential of torezolid.

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