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The rationale for use of linezolid (L) and rifampicin (R) combinations to prevent selection of resistant Staphylococcus aureus mutants: multiple-dose simulation using an in-vitro dynamic model

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Background: Based on our studies with L-exposed *S. aureus* in an *in vitro* dynamic model, "anti-mutant" ratios of the 24-hour area under the concentration-time curve (AUC) to the MIC may or may not be attainable at clinical doses. In the latter case, the use of L in combination with another anti-staphylococcal agent might be useful. To explore if combinations of L with R are able to restrict *S. aureus* resistance, the enrichment of L- and R-resistant mutants was studied by simulating single (L or R) and combined (L+R) treatments at therapeutic and sub-therapeutic AUCs.

Material/methods: Five-day treatments of a clinical *S. aureus* isolate (MIC_L 2 µg/ml; MIC_R 0.016 µg/ml) with twice daily of L and once-daily of R were simulated at therapeutic AUCs (240 and 60 mg×h/l – regimens L240 and R60, respectively) and sub-therapeutic AUCs (120 and 15, 30 mg×h/l – regimens L120 and R15, R30, respectively). Simulated combined treatments were L240+R15, L240+R30 and L240+R60 and L120+R15, L120+R30 and L120+R60. The mutant prevention concentrations (MPCs) were determined for L (MPC_L) and R (MPC_R) and for L+R (MPC_{L+R}). L-to-R concentration ratios were chosen as AUC ratios used in pharmacokinetic simulations: 2:1 (L120+R60), 4:1 (L120+R30 and L240+R60), 8:1 (L120+R15 and L240+R30) and 16:1 (L240+R15).

Results: *S. aureus* mutants resistant to 2× and 4×MIC of L and to 2×, 4×MIC, 8× and 16×MIC of R were enriched in all single treatments because simulated L concentrations were below the MPC_L (10 µg/ml) for most or the entire dosing interval while R concentrations never reached the MPC_R (1024 µg/ml). In contrast, there was no enrichment of L-resistant mutants in combined treatments when L

concentrations were above the MPC_{L+R} (2.5-3.1 µg/ml expressed as L concentration, regardless of the L-to-R concentration ratio) over the entire dosing interval. Furthermore, using L+R combinations R-resistant mutants were not enriched during the treatments but they regrew subsequently. This can be explained by abruptly decreased MPC_{L+R} (1.35, 0.78, 0.31 and 0.16 µg/ml expressed as R concentration at the L-to-R ratios of 2:1, 4:1, 8:1 and 16:1, respectively) that led to longer times above the MPC_{L+R} (39-56% of the dosing interval).

Conclusions: Full suppression of L-resistant and restriction of R-resistant *S. aureus* mutants exposed to L+R combinations were consistent with lowering the MPC_{L+R} as compared to MPC_L and MPC_R individually. Determination of the MPC at pharmacokinetically-based antibiotic concentration ratios may be useful to predict *S. aureus* resistance in combined treatments with antibiotics.