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Minocycline and rifampicin combination therapy for treatment and prevention of emergence of resistance in MRSA

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Background: MRSA is a leading cause of life-threating infections. In recent years decreased susceptibility to many first-line therapies has been observed, including daptomycin and vancomycin. Rifampicin has been used in combination with glycopeptides to treat MRSA infections successfully, particularly where deep tissue penetration is required such as in bone and joint infections. Long-acting tetracyclines such as minocycline have high oral bioavailability, tissue penetrance, and *in-vitro* anti-staphylococcal activity including against MRSA. Minocycline also exhibits synergy with rifampicin *in-vitro* against MSSA and MRSA. A murine PK-PD study was performed to examine the combination of minocycline and rifampicin for MRSA infection.

Material/methods: A murine thigh-infection model of MRSA was used. Mice were infected with 1 x 10^5 CFUs of MRSA strain 43456 in each thigh. Treatment commenced 2 hours post-inoculation with combinations of minocycline 10, 25, and 75 mg/kg/day Q6h and Q8h IV and rifampicin 10, 50, and 100 mg/kg/day q24h IV. Mice were sacrificed at 26, 50, 74, and 98 hours post-inoculation and thigh homogenates were quantitatively cultured on CLED media, CLED containing 32 mg/L minocycline, -containing and CLED containing 8 mg/L rifampicin. A final set of plates containing both 32 mg/L minocycline and 8 mg/L rifampicin were used. Minocycline and rifampicin plasma concentrations were analysed using LC/MS/MS. Concentrations were determined at 0.5, 2, 4, 6, and 26 hours after a single IV dose in separate experiments. A computational model using Pmetrics was employed to examine the effect of drug-exposure on susceptible MRSA killing and the emergence of resistance. Drug-drug interactions were modelled using a Greco model implemented within the differential equations.

Results: Individual posterior fits of the model to both PK and PD data were satisfactory. Rifampicin and minocycline were synergistic in killing susceptible MRSA (alpha=3.10, CI=2.71, 3.51) and minocycline-resistant MRSA (alpha=3.8, CI=3.43, 4.26) but antagonistic in suppression of rifampicin-resistant MRSA (alpha=-3.00, CI=-2.51, -3.49). PK-PD relationships were not examined on resistance to both rifampicin and minocycline since few isolates were observed. All treatment groups exposed to rifampicin as monotherapy or in combination lead to amplification of rifampicin-resistant mutants. This was incompletely suppressed with the addition of minocycline.

Conclusions: Minocycline and rifampicin combination therapy in a murine thigh-infection model of MRSA shows *in-vivo* synergy in killing susceptible isolates but rifampicin resistance emerged in all treatment groups exposed to rifampicin.