Activity of Friulimic B Against Glycopeptide and Daptomycin Non-susceptible S. aureus

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Introduction

Friulimic B (FR), an acidic cyclic lipopeptide intended for therapy of severe drug-resistant Gram-positive infections, is structurally similar to daptomycin (DAP) with a different molecular target. We tested FRI, DAP, vancomycin (VAN), teicoplanin (TEC) quinupristin/dalfopristin (Q/D), linezolid (LIN) against a spectrum of 19 mostly difficult to treat S. aureus strains and one DAPR VRE strain.

Methods: Three DAPR clinical strains (1 from Hershey which developed from MRSA to VISA while the patient was on VAN) had DAP MICs ≥4 µg/ml and 9 lab DAPR clones obtained by multistep R selection had DAP MICs >32 µg/ml. VAN-non-S strains were 3 VRSA and 2 VISA. MIC was for CLSI agar dilution (+ CaCl2 for FRI, DAP); Time-kills were in CAMHB (CLSI), final inocula 5 x 105 to 5 x 106 cfu/ml. In addition a DAPR clinical E. faecium was isolated in the analysis.

Results: MICs (µg/ml) against the 5 VAN-MRSA were: FRI, VAN, TEC, Q/D 0.5-4 µg/ml; VAN MICs (µg/ml) against 9 DAPR strains were 4-16 (FRI), 2-16 (VAN), 2-32 (TEC), 0.125-0.5 (Q/D); LIN was equal to 1 µg/ml against all strains. FRI MICs were 4-16 µg/ml. MICs of LIN and VAN were >64 µg/ml for those strains. VAN MICs were >64 µg/ml, a value defined as non-susceptible (VAN RS). MICs of LIN and VAN were >64 µg/ml for those strains.

Conclusions: FRI and DAP were very active against VRSA (0.5 - 4 µg/ml); MICs against DAPR-VRSA were 2-16; 4-8 µg/ml respectively. FRI was cidal against 7/9 of DAPR and reduced the CFU of the DAPR E. faecium isolate by 99% after 24 hrs at 16 µg/ml (8 x MIC).

Fig. 1: Friulimic B

Fig. 2: Selected kill curves

Table 1: MICs (µg/ml) of all agents against strains tested

Table 2: Results of time-kill experiments

Conclusions

• Standard MRSA strains have good susceptibility to friulimic B and to daptomycin.
• Strains ('HISA') with reduced susceptibility to all high molecular weight inhibitors irrespective of molecular mode of action were observed.
• The mechanism behind HISA could be thickened cell wall, as first described by Hirata, Cui, and co-workers.
• Kill kinetics of friulimic B and daptomycin were similar relative to MICs.
• Friulimic B at 8 x MIC led to a 24 hrs CFU reduction by 99% for a daptomycin resistant VRE isolate.