ABSTRACT

BACKGROUND

Omadacycline is a novel amiromycline antibiotic in development for acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP). The goal of the study was to determine the PK/PD targets in the murine thigh infection model against a diverse group of SA pathogens including MRSA and MSSA.

METHODS

Ten SA strains were selected. MICs were determined using CLSI methods. Single dose phosphate buffered saline (PBS) or saline plasmid DNA was injected intramuscularly into the thigh of isoflurane anesthetized mice. Four broth cultures were grown overnight to log phase to produce an inoculum of 6.5 log10 CFU/ml compared to untreated controls. Stasis and 1-log10 CFU/ml (from start of therapy) were observed against each strain. The AUC/MIC index was calculated using the Hill Emax equation. The total drug AUC/MIC associated with each endpoint were calculated for each strain.

RESULTS

Omadacycline demonstrated potent in vivo activity in a diverse group of SA pathogens including MRSA strains. Stasis 24 h AUC/MIC targets were approximately 22 ± 4.28. This is very similar to previous studies of omadacycline against pre-incubation (MIC50, 3.1 µg/ml) and other PK/PD evaluations of tetracycline-class antibiotics. 1-log10 targets were only 2-3 fold more than stasis targets for each strain. This data should provide useful in the dose-regimen optimization of omadacycline.

METHODS

Strains and susceptibility testing: 10 S. aureus strains were utilized including ATCC and clinical isolates as well as 6 MSSA and 4 MRSA (see Table 1). All isolates were tested in accordance with CLSI methods. Plates were read separately in duplicate.

Omadacycline Pharmacokinetics: Pharmacokinetic studies in mice were performed and published previously from this study was used to model AUC/MIC exposures. Protein binding of omadacycline is negligible and therefore total drug concentrations were utilized in all calculations.

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RESULTS

Omadacycline demonstrated potent in vivo activity in a diverse group of SA pathogens including MRSA strains. Stasis 24 h AUC/MIC targets were approximately 22 ± 4.28. This is very similar to previous studies of omadacycline against pre-incubation (MIC50, 3.1 µg/ml) and other PK/PD evaluations of tetracycline-class antibiotics. 1-log10 targets were only 2-3 fold more than stasis targets for each strain. This data should provide useful in the dose-regimen optimization of omadacycline.

CONCLUSION

1) Omadacycline demonstrated potent in vitro and in vivo activity against a diverse group of MSSA and MRSA clinical strains.

2) The exposure-response relationship was well described by AUC/MIC (p2 = 0.92). The exposure-response relationship was well described by AUC/MIC (p2 = 0.92).

3) The median stasis AUC/MIC target was 22 and median 1-log10 kill AUC/MIC target was 58. These values are similar to previous studies of omadacycline against S. pneumoniae as well as previous studies with other tetracycline derivatives.

4) Interestingly, there was evidence of enhanced efficacy against MRSA strains in this study as the median values were significantly different for stasis (MRSA stasis AUC/MIC of 18, MSSA stasis AUC/MIC of 20, p<0.05 by Mann-Whitney Rank Sum). These differences were small and not significant for median 1-log10 kill targets (MRSA 1-log10 kill, AUC/MIC of 55, MSSA 1-log10 kill, AUC/MIC of 60, p=0.48).

5) These studies should prove very useful in continued clinical development and optimization of omadacycline for S. aureus infections including designing optimal dosing strategies as well as preliminary breakpoints.