**Abstract**

Background: MRSA, a prevalent pathogen of hospital and community-acquired infections, can be difficult to treat due to resistance. Recently, resistance has emerged to commonly utilized anti-MRSA agents (e.g., linezolid [LZD], daptomycin [DAP], and vancomycin [VAN]). This makes the study of new agents like CEM-102 (fusidic acid) important in combating emerging drug-resistant MRSA. The objective of the present study was to evaluate the in vitro activity of CEM-102 against prevalent community-acquired, hospital-acquired, and epidemic MRSA clones.

**Methods:** 56 MRSA from the NARSA and Eurofins Medinet repositories were tested for their susceptibility to CEM-102 and comparators (VISA/VRSA isolates) according to current CLSI guidelines. Isolates included those with new resistance phenotypes (VISA/VRSA). MIC90 and MIC100 isolates were cultured from prevalent community (USA2000/USA100), hospital (USA100/USA600), and epidemic clones (e.g., Banter, UK-EMRSA-15/16).

Results: Against the selected resistant MRSA, CEM-102 had an MIC range of 0.06-8 μg/mL, with an MIC90 of 0.12 μg/mL. With the exception of 1 VISA isolate (with an MIC of 1 μg/mL), 2 DAP NS isolates (with MICs of 4 μg/mL), and 1 LZD NS isolate (with an MIC of 8 μg/mL), CEM-102 MICs were 0.06-0.12 μg/mL, against MRSA with rare but emerging resistance phenotypes. Against a subset of 10 community, 10 hospital, and 5 epidemic clones, CEM-102 MICs were 0.06-0.12 μg/mL.

Conclusions: CEM-102 had potent in vitro activity against MRSA NS to currently utilized agents (VAN, LZD, and DAP). CEM-102 was also active against USA100 and USA300 MRSA clones, demonstrating potential for the treatment of MRSA in the US.

**Introduction**

MRSA are commonly encountered clinically and, though rare, S. aureus with reduced susceptibility to other commonly used Gram-positive agents (vancomycin, linezolid/daptomycin) have emerged.

Fusidic acid is approved for use in Europe and is currently under development in the US for the treatment of acute bacterial skin (ABSSS) due to CEM-102, utilizing a novel oral dosing regimen designed to maximize bioavailability, increase coverage, and minimize resistance development.

This study evaluates the in vitro activity of CEM-102 and other Gram-negative agents against select resistant S. aureus isolates (e.g., VISA/VRSA, linezolid/daptomycin non-susceptible) and prevalent MRSA clones (e.g., USA100 and USA300).

**Materials and Methods**

- Clinical S. aureus isolates non-susceptible to currently utilized Gram-positive agents were identified from the Eurofins Medinet Repository (Chantilly, VA) and Eurofins Medinet (Chantilly, VA).
- Genetically characterized MRSA (PFGE type USA2000/USA100), hospital-acquired isolates (PFGE type USA500/USA600), and epidemic clones (PFGE type Iberian; British/Sporean, etc.) were also selected from the Eurofins and NARSA repositories with the exception of isolates 10 (Japan). CEM-102 was evaluated for its in vitro activity against new resistance phenotypes and 7 global epidemic strains, 5 isolates were of US origin.
- Selected-resistant S. aureus isolates were tested for susceptibility to CEM-102 and comparator agents by broth microdilution in accordance with CLSI M45-A3 and EUCAST breakpoint criteria.

**Results**

- Against the pre-selected resistant S. aureus evaluated, CEM-102 had an overall MIC90 of 0.12 μg/mL, several fold lower than the other evaluated agents (Table 1).
- Among the pre-selected resistant S. aureus and MRSA clones, 25% were VISA, 9% were VRSA, 13% were daptomycin non-susceptible, and 13% were linezolid-resistant (Table 1).
- Based on overall MIC distribution (Figure 1A), CEM-102 typically had an MIC of ≤0.12 mg/mL (91%), with few isolates (5%) having MICs >1 μg/mL, and no isolates having a CEM-102 MIC exceeding 8 μg/mL (10-fold lower than the 80 μg/mL maintained in the serum during the proposed CEM-102 dosing regimen).
- The CEM-102 MIC distribution was not notably altered by evaluated resistance phenotype or genotype (Figure 1B), though for the three isolates with CEM-102 MICs of 4-8 μg/mL, two were daptomycin non-susceptible and one was linezolid resistant (Table 3).
- The increased potency of CEM-102 relative to the other agents against the evaluated isolates was apparent by plotting cumulative susceptibility against MIC (Figure 2).
- Evaluated VISA/VRSA isolates (Table 2), though largely susceptible to CEM-102, were commonly resistant to other evaluated classes of agents.
- Hospital-acquired (HA-MRSA), community-acquired (CA-MRSA), and epidemic clones were 100% susceptible to CEM-102, including isolates with resistance across several classes of evaluated agents (e.g., USA100/USA600) (Table 4).

**Conclusions**

- CEM-102 (Fusidic acid) had potent in vivo activity against selected S. aureus with resistance to currently utilized Gram-positive active agents.
- CEM-102 was also active against clinical isolates of prevalent epidemic, hospital-acquired, and community-acquired clones of MRSA.
- The activity profile of CEM-102 which includes commonly encountered clinical MRSA/VRSA isolates was supported by NIAID.

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