E-101, a novel first in class topical anti-infective, maintains a high degree of potency in vitro against problem-resistant clinical pathogens (ESKAPE pathogens)

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ABSTRACT

Objective: E-101, a topical anti-infective which utilizes myeloperoxidase (MPO) for the generation of reactive oxygen species (ROS), is being studied for the prevention of surgical site infections. Infections caused by antibiotic resistant pathogens have become increasingly difficult to treat and are frequently difficult to predict. This study evaluates the activity of E-101 against highly resistant “ESKAPE” pathogens (vancomycin-resistant E. faecium [VRE], Enterococcus spp. (VRE), methicillin-resistant S. aureus [MRSA], K. pneumoniae [NDM-1], A. baumannii, P. aeruginosa, and carbapenemase producing P. aeruginosa). Methods: E-101 activity was evaluated using a modified broth microdilution method based on CLSI M7 guidelines. Modifications included serial dilution of enzyme (MPO) and media delivery in solutions containing enzyme substrate. E-101 MICs represent mg/mL. Comparisons (currently marketed agents and phenotypic markers) were tested in accordance with CLSI M7 and MDR. 101 non-duplicate clinical isolates were selected based on resistance phenotype for evaluation to include the “ESKAPE” phenotypes noted above.

Results: Against VRE, E-101 had an MIC50/MIC90 of 0.008-0.015 mg/L. Against S. aureus consisting of vancomycin susceptible isolates, hospital and community acquired MRSA, VISA, and VRE-1, E-101 had an MIC50/MIC90 of 0.008-0.015 mg/L, with MICs correlating 0.008 mg/L. E-101 had an MIC50 and MIC90 of 0.03 mg/L against ESBL, KPC, VRE, and MRSA; K. pneumoniae, with an MIC50 and MIC90 of 0.06 mg/L, against E. cloacae, MRSA, P. aeruginosa, and K. pneumoniae. Against MRSA and MDR isolates, E-101 activity against this cadre of multi-resistant pathogens demonstrates an excellent in vitro potency. E-101 potency against these highly resistant isolates was equivalent to that observed for E-101 during recent surveillance where isolates against ESBL [ESBL]/carbapenemase producing P. aeruginosa (VRE) were infrequently or not encountered.

Conclusions: E-101 was potent against prevalent HA-MRSA and CA-MRSA clones. This attribute highlights the utility of E-101 for the treatment of other superficial infections caused by resistant organisms.

BACKGROUND

• E-101 is a novel myeloperoxidase (MPO)-mediated antimicrobial. Once activated, E-101 generates oxidative products which damage bacterial cells if MPO, halide and a source of hydrogen peroxide are present (Figure 1)

• E-101 is currently undergoing clinical development for the prevention of surgical site infections in Europe and the US

• “ESKAPE” pathogens (Boucher et al, CID 2009;48:1) include pathogens with problematic resistance:
  - E. faecium (VRE)
  - S. aureus (MRSA and MDR)
  - K. pneumoniae (ESBL, KPC)
  - A. baumannii (MDR)
  - P. aeruginosa (MDR)
  - E. cloacae (AmpC)

• This study evaluates the in vitro activity of E-101 against “ESKAPE” pathogens, including those with emerging resistance phenotypes.

METHODS

• Clinical isolates included those pre-selected for a particular resistance phenotype based on test history and genetically characterized isolates were selected from both the Eurofins and NARSA repositories (Table 1).

• Susceptibility of isolates to E-101 was determined using a modified broth microdilution method based on CLSI M7 guidelines. Modifications included diluting E-101 enzyme solution containing MPO in 2x saline-adjusted Mueller-Hinton broth in the panel, and delivering the inoculum at 2x final concentration in 2x saline substrate solution to achieve a final concentration of 1x E-101, 1x substrate solution, and 5x 10CFUs/mL. Immediately post-incubation, E-101 begins to generate reactive oxygen species. MICs are reported based on mg/mL, NPO in E-101.

• Isolates were concurrently tested against relevant comparators in accordance with CLSI M7.

CONCLUSIONS

• The emergence and spread of resistance combined with the increasing prevalence of multi-drug resistance among ESKAPE pathogens has left relatively few effective therapeutic options for the treatment of drug resistant infections

• These developments highlight the need for new agents active against these resistant organisms (further illustrated by the recent emergence and spread of KPC and NDM-1 carbapenemases)

• E-101, currently undergoing evaluation for topical prevention of surgical infections, is a novel agent with multiple mechanisms of action that maintains its activity against ESKAPE pathogens with challenging resistance phenotypes

TABLE 1. Evaluated ESKAPE pathogens

<table>
<thead>
<tr>
<th>Organism/Phenotype</th>
<th>N</th>
<th>MIC (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA-MRSA</td>
<td>15</td>
<td>0.015-0.032</td>
</tr>
<tr>
<td>VISA</td>
<td>10</td>
<td>0.015-0.032</td>
</tr>
<tr>
<td>MRSA (NDM-1)</td>
<td>10</td>
<td>0.03-0.06</td>
</tr>
<tr>
<td>MDR (KPC)</td>
<td>15</td>
<td>0.12-0.12</td>
</tr>
<tr>
<td>ESBL</td>
<td>15</td>
<td>0.12-0.12</td>
</tr>
<tr>
<td>AmpC</td>
<td>15</td>
<td>0.06-0.12</td>
</tr>
</tbody>
</table>

ACKNOWLEDGEMENTS

This study was supported by a grant from Exoxemis, Inc. Eurofins would like to acknowledge Parvez Gohain, GRAVIT, Shafy & Usher, for their work on this project.

REFERENCES


TABLE 2. Activity profile of E-101 against evaluated ESKAPE pathogens

<table>
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FIGURE 1. Generation of reactive oxygen species from MPO: mechanism of action of E-101

E-101, a novel first in class topical anti-infective, maintains a high degree of potency in vitro against problem-resistant clinical pathogens (ESKAPE pathogens)

S. aureus

- Maintained potent MICs (0.015 mg/L or less) against a variety of problematic ESKAPE pathogens

- E-101 was active against prevalent HA-MRSA and CA-MRSA clones

Enterococci

- E-101 maintained potent activity against vancomycin resistant enterococci, with MICs in the 0.03-0.12 mg/L range

- E-101 MICs were 2-4 fold lower against vancomycin resistant E. faecium (0.03-0.06 mg/L relative to vancomycin resistant E. faecalis (0.06-0.12 mg/L)

Enterobacteriaceae

- Against various species and types of beta-lactamase producing Enterobacteriaceae, E-101 maintained potent MICs, including the recently emerged KPC producing K. pneumoniae

A. baumannii

- E-101 had MICs of 0.03 mg/L against all evaluated multi-drug resistant A. baumannii isolates.

P. aeruginosa

- Multi-drug resistant P. aeruginosa, E-101 was highly active with an MIC50 of 0.03 mg/L and an MIC90 of 0.06 mg/L.

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- These developments highlight the need for new agents active against these resistant organisms (further illustrated by the recent emergence and spread of KPC and NDM-1 carbapenemases)

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