Background
The 54th class of protein synthesis inhibitors demonstrates promising in vitro activity against Gram-positive and Gram-negative bacteria including resistant isolates (Jugalla et al., ICAAC 2011; 71,468; and Remy et al., ICAAC 2011, 71,469). 71 Further characterization the activity of the particularly potent pyrrolocytosine scaffold against Gram-positive proteins, a more in-depth evaluation was performed by a clinical laboratory on expanded numbers of compounds and isolates including Staphylococcus aureus (both methicillin-susceptible and resistant) and Enterococcus spp.

Methods
- Non-duplicate, globally diverse, clinically significant isolates were collected from 2009-2010 across the US. Included were 52 S. aureus (comprising 32 methicillin-susceptible S. aureus or MSSA, 30 methicillin-resistant S. aureus or MRSA, and overall 50% vancomycin-resistant MRSA), 30 Enterococcus faecalis (5% vancomycin-resistant Enterococci or VRE), and 30 Enterococcus faecium (20 VRE, 10 vancomycin-susceptible Enterococci). Twelve compounds from the pyrrolocytosine scaffold as well as additional control compounds were tested for antibacterial activity by the broth microdilution method as recommended by CLSI (M7-A8 and M100-S21).
- MICs of the RX-04 compounds against S. aureus were 0.06-4 µg/mL, and 0.12-32 µg/mL against E. faecium. MICs for the twelve compounds ranged from 0.25-4 µg/mL for S. aureus, 0.5-16 µg/mL for E. faecium, and 0.12-32 µg/mL against E. faecalis. Organisms exhibiting resistant phenotypes (MSSA/MDR or VRE) had MICs that were nearly identical to those that were characterized as susceptible.

Results
- New isolates from the pyrrolocytosine scaffold of RX-04 protein synthesis inhibitors demonstrate promising activity against a diverse collection of Gram-positive clinical isolates including those with resistant phenotypes such as MRSA and VRE. These compounds offer potential for the therapy of difficult-to-treat infections and warrant further investigation.

Abstract

Methods

Figure 1. Compounds from the Pyrrolocytosine Scaffold of Protein Synthesis Inhibitors

Table 1. MIC values for RX-04 compounds against S. aureus, E. faecalis, and E. faecium.

Table 2. MIC values for commercial compounds against S. aureus, E. faecalis, and E. faecium.

Table 3. MICs for commercial compounds against S. aureus, E. faecalis, and E. faecium.

Table 4. Pyrrolocytosines demonstrate promising antibacterial activity against E. faecalis and E. faecium.

Table 5. RX-04 compounds are highly potent against S. aureus, including MDR strains.

Figure 2. Compounds from the Pyrrolocytosine Scaffold of Protein Synthesis Inhibitors

Results

Twelve compounds from the pyrrolocytosine scaffold of the RX-04 program were tested for antibacterial activity against 60 isolates each of S. aureus and E. faecium. These strains were unique, clinically significant isolates collected from 2009-2010 across the U.S. The S. aureus isolates consisted of 22 methicillin-susceptible MSSA and 38 MRSA strains. Over 50% of the 60 S. aureus isolates exhibited an MDR phenotype, defined as demonstrating resistance to three or more of the following compounds: tetracycline, chloramphenicol, gentamicin, levofloxacin, and trimethoprim/sulfamethoxazole. The 60 S. aureus isolates comprised 30 E. faecalis, of which two were VRE, and 30 E. faecium (66.7% VRE).

Susceptibility testing was performed according to CLSI recommendations 11 using frozen commercial panels (TREK Diagnostics, Cleveland, OH). Control compounds included ampicillin (for Enterococcus spp.), chloramphenicol, ciprofloxacin, erythromycin, levofloxacin, lincomycin, and vancomycin.

Conclusions

The RX-04 pyrrolocytosines tested in this study demonstrate activity against S. aureus and Enterococcus spp.

MCIs against S. aureus, including MDR isolates, and E. faecalis were equal to or lower than those for the commercial compounds.

Against the more challenging VRE strains, MCIs were similar to those of the marketed agents.

The RX-04 novel protein synthesis inhibitors merit further investigation as a potential treatment for resistant Gram-positive organisms, including those associated with HAI.

References


1 Rib-X Pharmaceuticals Inc., New Haven, CT. 2 Euroflins Medinet, Chantilly, VA.