Novel Ribosome Inhibitors are Efficacious in a Murine Peritonitis Model Caused by Different Bacterial Pathogens

A. MARRA, E. BORTOLON, D. HOLSTAD, Y. WU, H. JING and E. DUFFY
Rib-X Pharmaceuticals, Inc., New Haven, CA USA

Background
There is a dearth of novel antibacterial agents with which to treat serious Gram-positive and Gram-negative infections. We have used structure-based drug design to generate novel compounds in three scaffolds targeting the large subunit of the bacterial ribosome. 004 compounds demonstrated excellent antibacterial activity in vitro and were further studied in vivo. The goal of the preclinical study was to evaluate the efficacy of example compounds in a murine peritonitis model caused by a range of organisms.

Methods

- The peritonitis was induced by injecting bacteria into the peritoneal cavity. Therapy was administered at 30, 60, 36 and 4 hours post-infection, and isoelectric focusing was performed to examine the plasma pharmacokinetics of select compounds to determine the area under the concentration-time curve (AUC) at the efficacious levels. Such robust demonstrations of efficacy at low doses against a broad range of organisms bode well for these compounds, which would be particularly advantageous in combating treating nosocomial infections caused by both Gram-positive and Gram-negative bacteria. Further evaluation showed that these compounds could deliver efficacy and 100% protection with a single dose. For the other organisms, efficacy was observed at 24 hours post-infection.

- Compounds were examined by measuring optical density at 600 nm; for E. coli, tissue concentrations of drugs were obtained at various time points up to 6 hours post drug administration using an LC/MS/MS assay.

- Results

- Co-compounds were used to treat peritoneal neutrophils in vitro. Results demonstrated that the compounds evaluated were from one of scaffold P were more active against this strain, 0.25 – 0.5 µg/mL. Single-digit PD50s were observed for all compounds evaluated (Table 3).

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- Conclusions

- Antibacterial compounds from one of scaffold P demonstrate efficacy in an in vivo model. The results of this study suggest that antibacterial compounds from scaffold P demonstrate efficacy against a range of organisms and offer promise for the treatment of nosocomial infections caused by Gram-positive as well as Gram-negative bacteria.

Antibacterial agents to treat serious Gram-positive and Gram-negative infections often fail due to bacterial resistance, poor tissue penetration and toxicity. In vivo, new classes of compounds have the potential to provide new therapeutic options.

Poster F1-1854

Results

- Table 1 summarizes the results of the peritonitis model. The compounds were evaluated for their ability to reduce bacterial burdens in target tissues and protect mice against lethal challenge in a mouse peritonitis model caused by E. coli frozen stocks.

- Table 2 correlates the efficacy observed in this model with MIC and plasma AUC for these compounds.

- Figure 1F. Figure 1F shows the efficacy of RX-I316 in reducing bacterial burdens in target tissues and protecting mice against lethal challenge in a mouse peritonitis model caused by A. baumannii.

- Results

- Table 1

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<th>Compound</th>
<th>MIC (µg/mL)</th>
<th>PD50 (mg/kg)</th>
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- Table 2

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Introduction

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Figure 1

- Figure 1A: Graphs of efficacy for RX-I316 (A, B), RX-P569 titration (C, D) and RX-P724 titration (E, F). Results are displayed as log10 cfu/mL of peritoneal wash fluid and spleen homogenate samples following a single therapeutic dose. The dotted horizontal line represents the limit of detection and the arrows below the x-axis indicate dosing times.

- Figure 1B: PRISM graphs of efficacy for RX-I316 (A, B), RX-P569 titration (C, D) and RX-P724 titration (E, F). Results are displayed as log10 cfu/mL of peritoneal wash fluid and spleen homogenate samples following a single therapeutic dose. The dotted horizontal line represents the limit of detection and the arrows below the x-axis indicate dosing times.

- Figure 1C: Graphs of efficacy for RX-I316 (A, B), RX-P569 titration (C, D) and RX-P724 titration (E, F). Results are displayed as log10 cfu/mL of peritoneal wash fluid and spleen homogenate samples following a single therapeutic dose. The dotted horizontal line represents the limit of detection and the arrows below the x-axis indicate dosing times.

- Figure 1D: Graphs of efficacy for RX-I316 (A, B), RX-P569 titration (C, D) and RX-P724 titration (E, F). Results are displayed as log10 cfu/mL of peritoneal wash fluid and spleen homogenate samples following a single therapeutic dose. The dotted horizontal line represents the limit of detection and the arrows below the x-axis indicate dosing times.

- Figure 1E: Graphs of efficacy for RX-I316 (A, B), RX-P569 titration (C, D) and RX-P724 titration (E, F). Results are displayed as log10 cfu/mL of peritoneal wash fluid and spleen homogenate samples following a single therapeutic dose. The dotted horizontal line represents the limit of detection and the arrows below the x-axis indicate dosing times.

- Figure 1F: Graphs of efficacy for RX-I316 (A, B), RX-P569 titration (C, D) and RX-P724 titration (E, F). Results are displayed as log10 cfu/mL of peritoneal wash fluid and spleen homogenate samples following a single therapeutic dose. The dotted horizontal line represents the limit of detection and the arrows below the x-axis indicate dosing times.

- Figure 1G: Graphs of efficacy for RX-I316 (A, B), RX-P569 titration (C, D) and RX-P724 titration (E, F). Results are displayed as log10 cfu/mL of peritoneal wash fluid and spleen homogenate samples following a single therapeutic dose. The dotted horizontal line represents the limit of detection and the arrows below the x-axis indicate dosing times.

- Figure 1H: Graphs of efficacy for RX-I316 (A, B), RX-P569 titration (C, D) and RX-P724 titration (E, F). Results are displayed as log10 cfu/mL of peritoneal wash fluid and spleen homogenate samples following a single therapeutic dose. The dotted horizontal line represents the limit of detection and the arrows below the x-axis indicate dosing times.